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Health Assessment Document for Chromium

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Report

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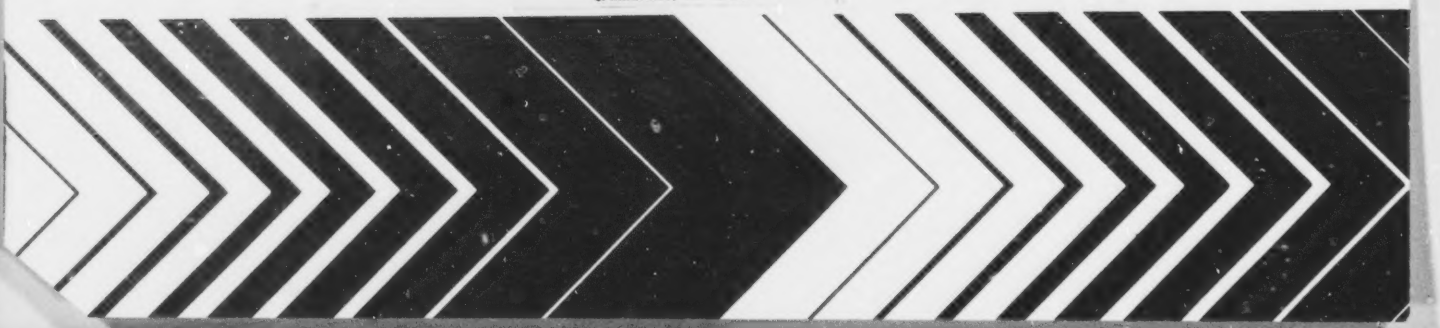

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16. ABSTRACT

The full document represents a comprehensive data base that considers all sources of chromium in the environment, the likelihood for its exposure to humans, and the possible consequences to man and lower organisms from its absorption. This information is integrated into a format that can serve as the basis for qualitative and quantitative risk assessments, while at the same time identifying gaps in our knowledge that limit accurate health assessment. Thus, it is expected that this document may serve the information needs of other government agencies and the private sector that may be involved in decision making and regulatory activities.

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Final Report

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
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Research Triangle Park, North Carolina 27711

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DISCLAIMER

This document has been reviewed in accordance with United States Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a "source document" for EPA use. The health assessment document was originally developed for use by the Office of Air Quality Planning and Standards to support decision-making regarding possible regulation of chromium as a hazardous air pollutant. However, the scope of this document has since been expanded to address multimedia aspects.

In the development of the assessment document, the scientific literature has been inventoried, key studies have been evaluated and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses are placed in perspective with observed environmental levels.

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The Office of Health and Environmental Assessment (OHEA) of U.S. EPA is responsible for the preparation of this health assessment document.

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1. INTRODUCTION

The 1970 Clean Air Act and its 1977 amendments mandate EPA to regulate, under Section 112, those pollutants that "may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness." It also states that EPA must regulate, under Section 111 (d), those pollutants that "may reasonably be anticipated to endanger public health or welfare."

For this reason, the Office of Air Quality Planning and Standards has requested that the Office of Health and Environmental Assessment prepare a scientific assessment for chromium so that it can be determined whether the regulation would be warranted under these sections of the Clean Air Act, since human exposure to chromium has been a matter of public health concern. Therefore, this chromium document will serve as a scientific data base for regulatory decision making by the agency. The health assessment document should represent an interpretive summary of relevant studies rather than a compendium of all available papers.

The present document represents a comprehensive data base that considers all sources of chromium in the environment, the likelihood for its exposure to humans, and the possible consequences to man and lower organisms from its absorption. This information is integrated into a format that can serve as the basis for qualitative and quantitative risk assessments, while at the same time identifying gaps in our knowledge that limit accurate health assessment at this time. Thus, it is expected that this document may serve the information needs of other government agencies and the private sector that may be involved in decision making and regulatory activities.

2. SUMMARY AND CONCLUSIONS

2.1. INTRODUCTION

Trivalent Chromium (Cr III) is considered an essential micro-nutrient at relatively low levels, largely because chromium deficiency results in a buildup of glucose in the blood. At much higher levels, certain hexavalent chromium (CrVI) compounds are known to be carcinogens. Thus, chromium is unique among the metallic elements, given its paradoxical roles in both nutrition and carcinogenesis. The seemingly contradictory information on the effects of chromium is being clarified through increasing understanding of the role of the differing oxidation states and types of chromium compounds, which apparently determine the relative risks and benefits to human health of chromium in its various forms.

In the ambient environment, however, most of the monitoring information has provided only total elemental chromium levels. Outside of occupational settings, only limited information exists on the types of chromium compounds to which the public is exposed, although the trivalent form is known to be predominant. The assessment which follows focuses on several key areas which bear on the kind and extent of effects associated with chromium compounds: sources and concentrations of important chromium compounds (particularly Cr(III) and Cr(VI)); measurement methods; pharmacokinetics and essentiality; toxic effects in man and animals; and carcinogenic risks.

2.2. FORMS, SOURCES AND CONCENTRATIONS OF CHROMIUM

Chromium is a metallic element which occurs in nature primarily as the mineral chromite; elemental chromium does not occur naturally. Chromium exists in four oxidation states, but only two of them, Cr(III) and Cr(VI), appear to be important, owing to their predominance and stability in the ambient environment. All forms are influenced greatly by pH, which affects the solubility and subsequent reactivity of chromium ions. Trivalent chromium is chemically basic, while hexavalent chromium is acidic.

Trivalent chromium is the most stable oxidation state, and the most important chemically. Its foremost characteristics are its ubiquitousness in the environment as part of the earth's crust, and its tendency to form kinetically inert hexacoordinate complexes. It reacts with aqueous hydroxides to form insoluble chromium hydroxide. Hexavalent chromium is the second most stable state, but the most important toxicologically. It occurs rarely in nature, apart from man's intervention, because it is readily reduced to Cr(III) in the presence of organic matter. It is quite soluble, existing in solution as a complex anion. However, in certain soils and natural waters, it can remain unchanged for protracted periods of time.

Chromite ore is not mined in the United States, but Cr(VI) chemicals are produced from imported ores, amounting to 21% of total U.S. chromium consumption. Metallurgical processes constitute approximately 60%, and refractory uses about 18%. Little direct information exists on the speciation of chromium compounds in the environment, because of the limitations of existing measurement methods (as described below). Accordingly, knowledge of chromium chemistry and its sources must be relied on in estimating the relative ambient contribution of different species. Direct sources include chemical and refractory plants; indirect sources include fossil fuel combustion, waste incineration and cement plant emissions.

Some source categories are likely to emit both trivalent and hexavalent forms of chromium. These are steel, refractory, chemicals manufacturing, as well as sewage sludge and municipal incineration. Cooling towers and chrome plating facilities emit hexavalent chromium, and chromium ore refining, ferro-chromium production, cement production, and coal and oil combustion are likely to be sources of trivalent chromium. Maximum annual average ambient (total) chromium levels within 20 kilometers of these sources range from approximately 0.01-13.50 $\mu g/m^3$.

Background ambient air concentrations of total chromium have ranged from as low as 0.005 ng/m^3 (at the South Pole) to 1.1 ng/m^3 in other remote areas of the world. In the United States, recent monitoring of the ambient air in many urban and non-urban areas has shown total chromium concentrations averaging in the range of approximately 0.005-0.157 $\mu g/m^3$. The maximum 24-hour average concentration found for any one site was 0.684 $\mu g/m^3$ in the Baltimore, MD area. Because Cr(III) is highly stable and Cr(VI) reacts over time to form Cr(III), it is assumed that most chromium in ambient air occurs in the trivalent state. Monitoring of both the species and oxidation states of chromium in the ambient air should be a priority for future research.

The chromium concentration in U.S. waters varies with the type of surrounding industrial sources and the type of underlying soils. An analysis of approximately 4,000 tap water samples in representative U.S. cities showed chromium concentrations ranging from 0.4 to 8 ppb. Chromium levels in soil vary with soil origin and degree of contamination from anthropogenic sources. Tests on domestic soil have shown chromium concentrations ranging from an average of 14-70 ppm. Because the amount of chromium in food and food plants is relatively low, and because chromium does not appear to accumulate in mammalian systems, bioaccumulation in the soil-plant-animal system does not appear to be a significant exposure source.

2.3. MEASUREMENT METHODS

One of the main problems in assessing the effects of chromium on human health is the lack of adequate methods to measure the types and amounts of chromium compounds. Prior to 1978, urinary chromium levels fell within the range of 2 to 20 µg/ℓ. In 1971, radio-tracer experiments indicated that approximately 0.5-1% of the chromium was absorbed throught the digestive system. Accordingly, chromium excretion of 10 µg/day would correlate with a chromium intake of 1-2 mg/day. However, few diets contain more than 100 µg/day chromium; this anomaly was resolved by showing that the background collection capabilities of the analytical methods used to measure chromium (atomic absorption) were inadequate for chromium determinations.

Several methods are available for measuring elemental chromium in both environmental and biological samples. These include atomic absorption spectroscopy, instrumental neutron activation analysis, X-ray fluoroescence, and particle-induced X-ray emissions (PIXE). While these methods are sensitive to the ppb level, problems in sample collection, preparation and interferences are shared by all. In biological samples, neutron activation analysis data tend to be lower than atomic absorption and X-ray fluorescence data. In environmental samples, neutron activation analysis data are higher. Generally, a comparison of the results indicates that modified atomic absorption spectroscopy provides relatively reliable analyses. Another problem in chromium determination is the lack of adequate reference materials. Ideally, reference materials should match the samples to be analyzed with respect to chromium levels and each reference composition. Because the materials are not yet standardized, inter-laboratory comparisons are difficult.

Techniques for monitoring hexavalent chromium are also subject to considerable error. For example, although the OSHA colorimetric method is the most commonly used analytical tool, particularly in occupational settings, low sample recoveries have been reported in chromium levels of less than 10 µg.

2.4. PHARMACOKINETICS AND ESSENTIALITY

2.4.1. Absorption, Transport and Excretion. An understanding of the role of chromium as an essential nutrient and causative agent in toxicity and carcinogenicity requires knowledge of the rates of absorption, mechanisms of absorption, transport and organ distribution of the various chromium-containing compounds. There are three primary routes of entry for chromium into the human body. For most people, the gastro-intestinal (GI) tract is the primary route of uptake, while in occupational exposures the airways and skin are the most important routes of uptake. Rates of uptake in the GI tract depend on a number of different factors, such as the valence state of chromium in the compound, the water solubility of the compound and the passage of time through the tract. Uptake in the airways is also influenced by the particle size distribution of the inhaled aerosols, and on factors which govern the clearance time of the lung.

Limited work on humans has been carried out on the relationship between exposure to trivalent chromium compounds and lung uptake and urinary excretion of chromium. In one study on workers exposed to chromium lignosulfonate, it was demonstrated that while chromium in the chromium lignin was present in the trivalent state, it acted pharmacokinetically like water soluble Cr(VI) compounds. An average of 14 µg/ℓ of urine was excreted, at an atmospheric chromium lignin concentration of 50 µg chromium/m^3. One to two percent of the inhaled chromium was excreted in the urine.

For Cr(VI), the urinary chromium concentrations corresponding to an airborne concentration of 50 µg/m^3 Cr(VI) were 40 µg/ℓ in one study, and 10 to 20 μg/ℓ in another. It was noted that chromium-bearing particles stay longer in the airways in smokers than in non-smokers.

The established normal levels of chromium in whole blood and in serum have declined with time, reflecting the changes and improvements in analytical methods. In the airways and in the GI tract, soluble Cr(VI) compounds are apparently taken up by epithelial cells by simple diffusion through the plasma membrane. After entry, Cr(VI) reduction occurs from the action of enzymatically mobilized electrons, which are available from GSH, NADPH, and NADH. The reducing capacity inside the cell is limited, so that Cr(VI) and Cr(III) exist simultaneously inside the cytoplasm; Cr(VI) is then released from the cell by simple diffusion into the blood stream and taken up into blood cells. In spite of the refined methods of analysis available, a reliable range of normal blood chromium concentrations cannot be given with confidence. When using modern methods for analysis, the whole blood concentration may be suggested to be within the range of 0.5 to 3 ppb, while the serum level is probably below 0.2 ppb.

The chromium concentration in human tissues has been shown to decrease with increasing age. In contrast to this, chromium concentrations in the lung have been shown to increase with age. This increase in chromium content in the lungs may be due to deposition and retention of insoluble chromium-containing particles from the inhaled environmental air, as well as from tobacco smoke.

2.4.2. Essentiality of Chromium. Animal studies have demonstrated that chromium-deficient rodents gain less weight and have a shorter life-span than animals maintained on a diet containing adequate chromium values. Chromium deficiency results in glucose intolerance in rats. This intolerance can be reduced with dietary treatment with Cr(III). In humans, symptoms of chromium deficiency consist of glucose intolerance, weight loss and confusion. Those prone to chromium deficiency include the elderly, diabetics, pregnant women, malnourished children, offspring or siblings of diabetics and persons with early coronary heart disease. Although the exact level of chromium needed for good health is not known, the average American intake of 50 to 200 µg/day is considered adequate because at such levels symptoms associated with chromium deficiency are not observed. It should be noted that there is a considerable difference between the low levels of intake that are associated with nutritional deficiency and the high levels of exposure which are associated with toxic effects.

2.5. EFFECTS OF CHROMIUM ON BIOLOGICAL SYSTEMS AND HEALTH

2.5.1. Toxic Effects in Man and Animals. The effects of both Cr(III) and Cr(VI) have been studied in man and animals. Both long-term and short-term exposure conditions have been investigated, but most of the long-term exposures have focused on carcinogenic effects (discussed in Section 2.5.2. below).

The relative chemical inactivity of Cr(III) compared with Cr(VI) correlates with various acute toxicity studies on chromium salts. Oral LD_{50} (dose lethal to 50% of recipients) levels in rats have been reported to range from 135 mg/kg to 11,260 mg/kg for Cr(III). As seen in the previous section on pharmacokinetics, the relatively high amounts of Cr(III) which are required to cause death arise from the relative insolubility and poor intestinal absorption of most Cr(III) compounds. Unlike the trivalent compounds, those of Cr(VI) tend to cross biological membranes fairly easily, and are somewhat more readily absorbed through the gut or through the skin. The strong oxidizing powers of Cr(VI) compounds explain much of their irritating and toxic properties.

Exposure to Cr(VI) has been associated primarily with renal damage. For humans no quantitative evidence of acute toxcity through oral ingestion has been reported. In various animal species, single injections of 2 mg/kg caused cellular and structural damage in the kidneys.

The effects of chromium on the skin were recognized over 150 years ago. Many chromium compounds can damage the skin, but metallic chromium or chromium alloys are chemically inert and are not harmful. The effects of chromium compounds on the skin are caused primarily by direct contact. Most of the effects have occurred in occupational settings, and, as expected, with more men than women reporting effects. Cr(VI) derivatives can cause ulcers of the hands and accompanying perforations of the nasal septum. Allergic contact dermatitis may arise from exposure to either trivalent or hexavalent chromium, although hexavalent chromium is responsible for most of the reported cases. Cr(VI) penetrates undamaged skin, and subsequently reduces to Cr(III) which combines with proteins or other skin components to form a whole skin allergin.

Effects on the upper respiratory tract have been observed in workers in chromium-related industries. The major effects of chromium on this system include ulceration of the nasal septum, with subsequent perforation, and chronic rhinitis and pharangitis. Early studies indicated that approximately one-half to four-fifths of the workers in chromate plants had perforated nasal septa, at levels of exposure that approached 1 mg/m^3. Subsequent work indicated that chromic acid levels exceeding 0.1 mg/m^3 also caused perforated septums in some workers.

Limited work has been reported on reproductive effects of chromium. Cr(VI) and Cr(III) have been found to cross the placental barrier in animals (hamsters and mice) and enter the fetus during mid to late gestation. Fetal uptake of Cr(VI), however, was much greater than that of Cr(III). Developmental effects attributed to both Cr(VI) and Cr(III) differed between hamsters and mice, and included such external abnormalities as cleft palate and skeletal defects, and (in one study of a Cr(III) compound) neural tube defects. One researcher concluded that Cr(VI) occurred at sufficiently high fetal concentrations to cause direct effects on embryonic structures, but also questioned whether all of the teratogenicity and fetal toxicity associated with exposure to Cr(III) might be attributed to extra-embryonic effects, for example, those on placental tissues.

2.5.2. Genotoxicity, Carcinogenicity and Assessment of Risk.

2.5.2.1. GENOTOXICITY -- In recent years, much evidence has accumulated to show that compounds of chromium possess the ability to cause transformations and mutations, as evaluated in a wide variety of *in vitro* assays such as the reverse and forward mutation, gene conversion, and DNA modification tests. Genotoxic effects have been demonstrated primarily for chromium compounds containing the Cr(VI) species, including effects such as:

-- Mutagenic responses in bacterial strains.
-- Morphologic changes in mammalian fetal cells.
-- Cytogenic effects on mammalian bone marrow cells.
-- Increased gene conversion in yeast species.
-- Increased transformation frequencies in mammalian cells.
-- Chromosomal damage in cultures of human lymphocytes.

In general, soluble Cr(VI) compounds are less active in the presence of metabolic activating systems. The reduction of Cr(VI) to Cr(III) by cellular agents in metabolic activation systems, in part, explains the reduced mutagenic activity of Cr(VI) in the presence of such activating systems. Some recent evidence implicating both Cr(VI) and Cr(III) in induced mutagenesis has been reported in DNA interaction and DNA polymerase infidelity assays, and several tests with apparently pure Cr(III) samples have found chromosomal aberrations.

However, with the exception of hexacoordinate Cr(III) compounds, and Cr(III) compounds contaminated with Cr(VI), trivalent chromium is generally considered to be a relatively inactive genotoxic agent, owing to its inability to cross cell membranes.

2.5.2.2. CHROMIUM CARCINOGENESIS AND ASSESSMENT OF RISK -- The epidemiologic studies of chromate production workers have demonstrated an association of exposure to chromium compounds with respiratory cancer. Whether the association implicates hexavalent chromium (Cr VI) alone, or trivalent (Cr III) as well, is not definitively addressed by these studies. The strength of the association is evidenced by the high relative risks of lung cancer (e.g., a lung cancer mortality ratio of 29 was found in one study of chromate production workers), the consistency of results by different investigators in different countries, a dose-response relationship, and the specificity of the tumor site (i.e., the lung). Results of three epidemiologic studies of chrome pigment workers also provide suggestive evidence that these workers are at an elevated risk of lung cancer. One epidemiologic study of chrome pigment workers (Davies 1978, 1979) suggested that zinc chromate was carcinogenic while lead chromate was not. However, the usefulness of the data on the lead chromate pigment workers is limited by small sample size. Using the criteria of the International Agency for Research on Cancer (IARC), the epidemiologic studies of chromate production workers would be classified as showing sufficient evidence of carcinogenicity.

Several hexavalent chromium compounds have been shown to be carcinogenic in cancer bioassay studies. Only calcium chromate has consistently produced lung tumors in rats by several routes of administration. Other chromium compounds--strontium chromate, zinc chromate, sodium dichromate, lead chromate, lead chromate oxide, and sintered chromium trioxide--have produced local sarcomas or lung tumors in rats at the site of intrabronchial, intratracheal, intramuscular, subcutaneous and intraperitoneal application. Hexavalent chromium compounds have not induced lung tumors by inhalation; however, studies have not been reported in detail. Trivalent chromium compounds have not been reported to be carcinogenic by any route of administration. Animal cancer bioassay studies suggest that hexavalent chromium compounds (particularly soluble and sparingly soluble compounds) are probably the etiologic agent in chromium related human cancer. Under the IARC criteria, the animal bioassay studies would constitute sufficient evidence of the carcinogenicity of hexavalent chromium compounds.

Using the IARC classification scheme, the level of carcinogenic evidence available for the combined animal and human data would place hexavalent chromium (Cr VI) compounds into Group 1, meaning that there is decisive evidence for the human carcinogenicity of those compounds.

The lifetime cancer risk due to air containing 1 $\mu g/m^3$ of hexavalent chromium compounds is estimated to be 1.2×10^{-2}. This would place hexavalent chromium (Cr VI) in the first quartile of the 53 compounds evaluated by the CAG for relative potency.

3. BACKGROUND INFORMATION

3.1. CHEMICAL AND PHYSICAL PROPERTIES

Chromium was discovered in 1797 by the French chemist, Louis Vanquelin. Metallic chromium is steel gray in color, melts at 1857 ± 20°C, boils at 2672°C, and has a specific gravity of 7.20 at 28°C (Weast, 1980). As found in nature, chromium is a mineral mixture of four stable isotopes of mass numbers 50, 52, 53, and 54 (Cary, 1982).

The inorganic chemistry of chromium and its compounds has been extensively studied. However, its physical or chemical forms and the mode by which they are incorporated into biological systems are poorly characterized. Inorganic chromium compounds occur in valence states ranging from -2 to +6.

Chemically, the Cr(III) state is the most stable and important form of chromium. In neutral and basic solutions, Cr(III) forms binuclear and polynuclear compounds in which adjacent chromium atoms are linked through hydroxy-(OH) or oxo-(O) bridges. Interestingly, Cr(III) forms stable complexes with amino acids and peptides (deMeester and Hodgson, 1977; deMeester et al., 1977). Cr(III) also has a strong tendency to form hexacoordinated octahedral complexes with ligands, such as water, ammonia, urea, ethylenediamine, halides, sulfates, and organic acids. These relatively stable complex formations (Cotton and Wilkinson, 1972; Kiilunen et al., 1983) can prevent precipitation of Cr(III) at pH values at which it would otherwise precipitate.

Cr(VI) exists in solution as hydrochromate, chromate, and dichromate ionic species. The proportion of each ion in solution is dependent on pH. In strongly basic and neutral pHs, the chromate form predominates. As the pH is lowered, the hydrochromate concentration increases. At very low pHs, the dichromate species predominates. In the pH ranges encountered in natural water, the predominant forms are hydrochromate ions (63.6%) at pH 6.0 to 6.2 and chromate ion (95.7%) at pH 7.8 to 8.5 (Trama and Benoit, 1960). The oxidizing ability of Cr(VI) in aqueous solution is pH dependent. The oxidation potential of Cr(VI) increases at lower pHs. The ability of Cr(VI) to oxidize organic materials and the tendency of the resulting Cr(III) to form stable complexes with available biological ligands afford a reasonable mechanism by which chromium can interact with the normal biochemistry of man (Towill et al., 1978).

The physical properties of several environmentally significant trivalent chromium compounds are shown in Table 3-1. The same parameters for selected Cr(VI) compounds are shown in Table 3-2. It should be mentioned that there is considerable disagreement in the literature concerning the physical parameters given in Tables 3-1 and 3-2 and therefore these values should be accepted with reservation. The disagreement in the values is possibly due to the reactions of these compounds with other substances, namely with moisture and air at high temperatures, impurities, and structural and compositional changes occurring during the experimental determinations.

Reactions of Cr(III) in alkaline solution depend on the concentration of OH^- ions. When hydroxyl ions are added to Cr(III) solutions in quantities insufficient for precipitation, basic ions are formed, which then polymerize with the formation of hydroxy- or oxy-bridged compounds as shown below:

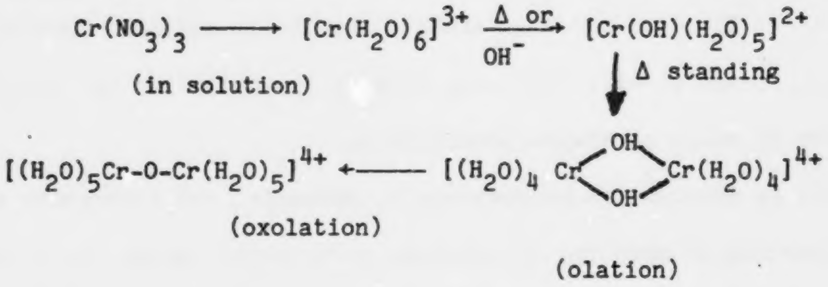

TABLE 3-1

Physical Properties of Selected Trivalent Chromium Compounds*

Compound	Formula	Density, g/cm^3	Melting Point, °C	Boiling Point, °C	Solubility in Water, g/100 mℓ
Chromic acetate	$Cr(CH_3COO)_3 \cdot H_2O$	NR	NR	NR	slightly soluble
Chromic chloride	$CrCl_3$	2.76 (15°C)	≈1150	1300 (sublimes)	insoluble
Chromic chloride, hexahydrate	$[Cr(H_2O)_4Cl_2]Cl \cdot 2H_2O$	1.76	83	NR	58.5 at 25°C
	$[Cr(H_2O)_6]Cl_3$	NR	NR	NR	soluble
Chromic formate, hexahydrate	$[Cr(HCOO)_3] \cdot 6H_2O$	NR	decomposes above 300	NR	soluble
Chromic oxide	Cr_2O_3	5.21	2266	4000	insoluble
Chromic phosphate, hydrated	$CrPO_4 \cdot 2H_2O$	2.42 (32.5°C)	NR	NR	slightly soluble
	$CrPO_4 \cdot 6H_2O$	2.121 (14°C)	100	NR	insoluble
Chromic sulfate	$Cr_2(SO_4)_3$	3.012	NR	NR	insoluble
Chromic sulfate, hydrated	$Cr_2(SO_4)_3 \cdot 15H_2O$	1.867 (17°C)	100	100(-100 H_2O)	soluble
	$Cr_2(SO_4)_3 \cdot 18H_2O$	1.7 (22°C)	100(-12H_2O)	NR	120 at 20°C

*Source: Weast, 1980; The Merck Index, 1976
NR = Not reported

TABLE 3-2

Physical Properties of Selected Hexavalent Chromium Compounds[a]

Compound	Formula	Density,[b] g/cm^3	Melting Point, °C	Boiling Point, °C	Solubility in Water, g/100 mℓ
Ammonium chromate	$(NH_4)_2\ CrO_4$	1.91_{12}	180 decomposes	NR	40.5 at 30°C
Ammonium dichromate	$(NH_4)_2Cr_2O_7$	2.155_{25}	180 decomposes	NR	30.8 at 15°C
Barium chromate	$BaCrO_4$	4.498_{25}	decomposes	NR	3.4×10^{-4} at 160°C
Chromium (VI) oxide	CrO_3	2.70_{25}	197	decomposes	67.45 at 100°C
Lead chromate	$PbCrO_4$	6.12_{15}	844	decomposes	5.8×10^{-6} at 25°C
Mercurous (I) chromate	Hg_2CrO_4	NR	decomposes	NR	very slightly soluble
Mercuric (II) chromate	$HgCrO_4$	NR	decomposes	NR	slightly soluble, decomposes
Potassium chromate	K_2CrO_4	2.732_{18}	971	NR	62.9 at 20°C
Potassium dichromate	$K_2Cr_2O_7$	2.676_{25}	398	500 decomposes	4.9 at 0°C 102 at 100°C
Sodium chromate	Na_2CrO_4	2.723_{25}	792	NR	87.3 at 30°C
Sodium dichromate dihydrate	$Na_2Cr_2O_7 \cdot 2H_2O$	2.348_{25}	84.6 (incongruent)	400 decomposes	180 at 20°C

[a] Source: Weast, 1980; Hartford, 1979

[b] The lower figures indicate the temperature (°C) at which the densities were measured.

NR = Not reported

Such ions are of the proper size to cross-link protein fibers and may play an important part in the chemistry of tanning. The single hydroxyl-bridged rhodo and erythro binuclear Cr(III) amine complexes also have been extensively studied (Veal et al., 1973; Cline et al., 1981).

When a sufficient amount of a base is added to Cr(III) salt solution, a hydrous oxide of indefinite composition, $Cr_2O_3 \cdot xH_2O$, is precipitated. On addition of more base to the hydrous oxide, the precipitate redissolves, probably due to formation of complex ions of the type $[Cr(OH)_x]^{3-x}$ (e.g., $[Cr(OH)_4]^-$, $[Cr(OH)_6]^{3-}$).

Cr(III) compounds are reduced to Cr(II) compounds by hypophosphites, electrolysis, or reducing metals, such as Zn, Mg, and Al in acid solution (although it should be noted that Cr(II) compounds are stable only in the absence of air). In basic solution, Cr(III) is readily oxidized to CrO_4^{2-} by hypochlorite, hypobromite, peroxide, and oxygen under pressure at high temperature. Heating of chromium compounds in air in the presence of alkalies also yields chromate. In acid solution, Cr(III) is harder to oxidize and needs strong oxidizing agents, such as concentrated $HClO_4$, sodium bismuthate, and permanganate.

All Cr(VI) compounds except CrF_6 are oxo-compounds. Cr(VI) rarely occurs in nature, apart from anthropogenic sources, because it is readily reduced by oxidizable organic matter. However, after it is introduced into water, Cr(VI) frequently remains unchanged in many natural water sources because of low concentration of reducing matter. Cr(VI) occurs most commonly in the form of chromate or dichromate, both of which are produced on a large scale in industry. The dissociation equilibrium of chromic acid solution indicates the weaker acidity of H_2CrO_4. The dissociation of $H_2Cr_2O_7$ appears to be that of a strong acid. Acid solutions of dichromate are powerful oxidizing agents:

$$Cr_2O_7^{2-} + 14H^+ + 6e^- \longrightarrow 2Cr^{+3} + 7H_2O, \ E° = 1.33V$$

Dichromate salts are the leading commercial form of Cr(VI).

3.2. PRODUCTION, USE, AND RELEASES TO THE ENVIRONMENT

The purpose of this document is to present available information relevant to human health effects that could be caused by this substance.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risks to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, a considerable effort will be undertaken to obtain appropriate information regarding sources, emissions and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

3.2.1. Production of Chromium Compounds. The industrial processes for the production of chromium metal and the various compounds have been described by Hartford (1979). A simplified flow chart depicting these processes appears in Figure 3-1.

There has been no mining of chromite ore in the United States since 1961. Chromium ore and ferrochrome alloys are imported mainly from the Soviet Union, South Africa, Turkey, and Zimbabwe.

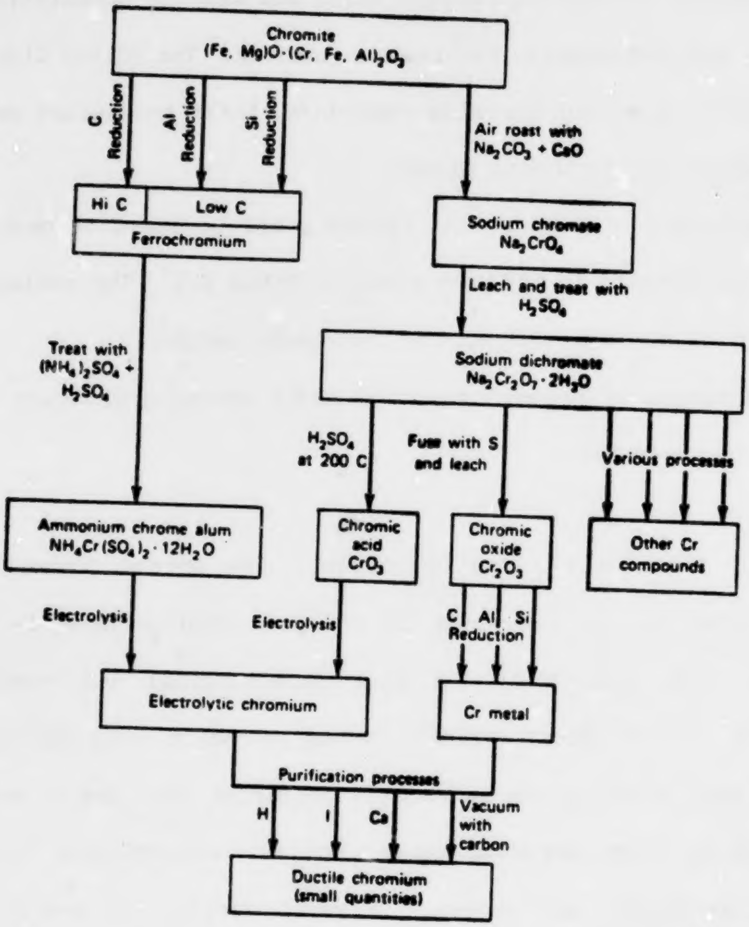
Chromite
(Fe, Mg)O·(Cr, Fe, Al)$_2$O$_3$
C Reduction
Al Reduction
Si Reduction
Air roast with Na$_2$CO$_3$ + CaO
Hi C
Low C
Ferrochromium
Sodium chromate
Na$_2$CrO$_4$
Leach and treat with H$_2$SO$_4$
Sodium dichromate
Na$_2$Cr$_2$O$_7$·2H$_2$O
Treat with (NH$_4$)$_2$SO$_4$ + H$_2$SO$_4$
H$_2$SO$_4$ at 200 C
Fuse with S and leach
Various processes
Ammonium chrome alum
NH$_4$Cr(SO$_4$)$_2$·12H$_2$O
Chromic acid
CrO$_3$
Chromic oxide
Cr$_2$O$_3$
Other Cr compounds
Electrolysis
Electrolysis
C Al Si
Reduction
Electrolytic chromium
Cr metal
Purification processes
H
I
Ca
Vacuum with carbon
Ductile chromium
(small quantities)

FIGURE 3-1

Simplified Flow Chart for the Production of Metallic Chromium and It Compounds From Chromite (Hartford, 1979)

The two primary industrial compounds of chromium made directly from chrome ores are sodium chromate and sodium dichromate. Secondary chromium compounds produced in substantial quantities include potassium chromate and potassium dichromate, ammonium dichromate, chromic acid, and various formulations of basic chromic sulfate used principally for leather tanning. The United Stated manufacturers of the three important chromium compounds, their production capacity, and the amount produced are discussed below.

The manufacturers of both sodium chromate and sodium dichromate and their annual production capacity in 1982 are given in Table 3-3. The estimated production capacity is based on a 100% sodium dichromate weight.

The manufacturers of chromic acid and their annual production capacity in 1982 are given in Table 3-4.

3.2.2. Uses of Chromium and Its Compounds. The United States consumption pattern of chromium and its compounds for the year 1979 is shown in Table 3-5.

It can be seen from Table 3-5 that metallurgical and chemical usages constituted 82% of the total United States chromium consumption in 1979. Metallurgical grade chromite ore is usually converted into one of several types of ferrochromium or other chromium metal that are alloyed with iron or other elements, such as nickel and cobalt. A great variety of useful steels are produced from these alloys. Because of their high melting points and chemical inertness, chromite ore and chrome alloys are used by the refractory industry in furnaces as linings, in the manufacture of furnace bricks, and as coating materials to close pores and to join bricks within the furnace. Other uses of chromite refractories include nonferrous alloy refining, glass making, and cement processing. The pattern of chromium consumption in the United States has been consistent over the last 20 years. However, the use of chromite and chrome

TABLE 3-3

Manufacturers and Their Production Capacities of Sodium Chromate and Sodium Dichromate[a]

Manufacturers	Annual Production Capacity in 1982, 10^3 metric tons
Allied Chemical Corp. Baltimore, MD	65
American Chrome and Chems., Inc. Corpus Christi, TX	45
Diamond Shamrock Castle Hayne, NC	94[b]
TOTAL	204

[a] Source: SRI International, 1982; 1982 U.S. Industrial Outlook, Chemical Marketing Reporter, 1982.

[b] Diamond Shamrock will increase capacity to 118,000 tons in January 1983.

TABLE 3-4

Principal United States Manufacturers of Chromic Acid[a,b]

Manufacturers	Annual Capacity in 1982, 10^3 metric tons[c]
Allied Chemical Corp. Baltimore, MD	21
Diamond Shamrock Corp. Castle Haynes, NC	24

[a] Source: SRI International, 1982; Hartford, 1979

[b] Data on actual production of chromic acid are held to be confidential to avoid disclosing proprietary information on individual companies.

[c] The estimates for production capacity are based on a 100% chromic anhydride (CrO_3) basis.

TABLE 3-5

United States Chromium Consumption Pattern in 1979[a]

	Quantity Consumed[b,c] 10^3 metric tons	% Fraction of U.S. Consumption
Metallurgical		
wrought stainless and heat resisting steels	235	44
tool steels	6	1.1
wrought alloy steels	44	8.1
cast alloy steels	15	2.7
alloy cast irons	8	1.4
nonferrous alloys	15	2.7
other	6	1.1
Total	329	61.0
Refractories		
chrome and chrome-magnesite	16	3.0
magnesite-chrome brick	23	4.2
granular chrome-bearing	42	7.8
granular chromite	16	3.0
Total	97	18.0
Chemicals		
pigments	29	5.4
metal finishing	24	4.4
leather tanning	18	3.3
drilling muds	5	0.9
wood treatment	7	1.3
water treatment	7	1.3
chemical manufacture	9	1.7
textiles	4	0.7
catalysts	<2	0.3
other	9	1.7
Total	114	21.0
Grand Total	540	100

[a] Source: Hartford, 1979, Mineral Commodity Summaries, 1980.

[b] Exclusive of scrap.

[c] Columns may not total exactly due to rounding.

alloys in the refractory industry is beginning to decline as open hearth furnaces are replaced by basic-oxygen furnaces (Hartford, 1979). In the future, growth in chromium usage is expected in the metallurgical and chemical sectors. A recent study (Morning, 1977) has projected a 3.4% growth annually in the United States chromium consumption, leading to a total chromium demand of 1 million tons (900,000 metric tons) in the year 2000.

The consumption pattern of imported chromium for metallurgical, refractory, and chemical usage is shown in Table 3-5. Chromium-containing pigments can be primarily classified into chromate color pigments based on lead chromate, Cr(III) oxide greens, and corrosion inhibiting pigments based primarily on zinc chromate. In metal finishing, chromic acid is used in chromium plating of metal surfaces. The chrome tanning of leather is one step in a complicated series of operations leading from the rawhide to the finished product. The annual consumption of hides by the leather industry is decreasing (Hartford, 1979), and the use of Cr(VI) compounds for tanning purposes may be on the decline. Chromium chemicals, such as chromium lignosulfonates, are used in drilling muds during the drilling of wells to combat fatigue corrosion cracking of drill strings (Hartford, 1979). Chromated copper arsenate is widely used as a wood preservative, especially in treating building lumber, and wood foundations. Chromates are used to inhibit metal corrosion in recirculating water systems, such as cooling towers, locomotives, and automobiles. Sodium dichromate and various chromic salts are employed in the textile industry to improve washfastness and to oxidize the dyed textile. A large number of chromium compounds are used as catalysts in various chemical reactions. Barium and calcium chromates are used as activators and dipolarizers in fused salt batteries. Chromium dioxide (CrO_2) is used as a ferromagnetic material in high-fidelity magnetic tapes.

3.2.3. Releases to the Environment. Although the chromium industry in the United States has adopted various pollution control measures, some release of chromium compounds into the environment is occurring. Chromium compounds from industrial operations enter the environmental air, water, and soil from several sources. Kilns, smelting furnaces, boilers, leaching tanks, open boiling vessels, plating tanks, and other installations emit dusts and mists containing chromium to the atmosphere.

Chromium is a trace component of coal and oil and is released to the atmosphere upon combustion of these fuels. Fly ash emitted from coal-fired power plants contain 10 to 600 ppm chromium, depending on the type of boiler firing (Block and Dams, 1976; Hock and Lichtman, 1982). For power plants equipped with electrostatic precipitators (ESP) to control particulate emissions, the total chromium concentration in the emission can be reduced (NAS, 1974). Rinaldi et al. (1980) have shown that the chromium concentration of particulates from controlled coal combustion may be higher than the chromium concentration of particulates from uncontrolled coal combustion, due to preferential chromium enrichment on small particles that escape the ESP device.

Wood contains chromium and it is likely that the burning of wood in fireplaces and campfires may contribute small amounts of chromium into the atmosphere. Forest fires would therefore be a potential non-anthropogenic source of atmospheric chromium (NAS, 1974). No estimate of the amount of chromium emitted from forest fires could be obtained. However, Lantzy and MacKenzie (1979) estimated chromium flux in the atmosphere from anthropogenic (industrial and fossil fuel) and non-anthropogenic (continental dust, volcanic dust, and volcanic gas) sources. The ratio of anthropogenic to non-anthropogenic atmospheric flux of chromium was estimated to be 1.61. Incineration of municipal refuse and sewage sludge is also expected to contribute small amounts of chromium into the atmosphere (Rinaldi et al., 1980; Fiscus et al., 1978).

It is now known that asbestos contains as much as 0.15% chromium (Towill et al., 1978). Thus asbestos mining and the wearing of vehicular brake linings represent potential sources of chromium in the atmosphere. Catalytic emission control systems in automobiles using copper chromite reduction catalysts represent another source of chromium emissions to the atmosphere (IARC, 1980). Also, when chromate chemicals are used as corrosion inhibitors in recirculating cooling waters, some chromate is lost to the atmosphere as mist.

According to a Radian Corporation (1984) report, United States industrial and inadvertent sources of chromium emissions into the atmosphere under existing controlled operations amounted to about 5,000 metric tons. Estimated amounts of atmospheric chromium emissions are shown in Table 3-6.

The geographical distribution of atmospheric chromium emissions in the United States is presented in Table 3-7. It is evident from Table 3-7 that the Great Lakes area, the Southeast and the East coast south from New York constitute the bulk of atmospheric chromium emissions in the United States.

Chromium compounds occur in a variety of industrial wastewaters and potentially may enter surface water and groundwater supplies. Wastewaters from electroplating operations, leather tanning, and textile manufacturing represent the types of chromium-containing streams that may ultimately enter surface and groundwaters (Hartford, 1979). It has been estimated that 220 metric tons/year are discharged in Southern California coastal waters (Schafer, 1977). Ottinger et al. (1973) estimated that 6200 metric tons of chromium are lost annually in the sludge of solvent-based paints and another 437 metric tons are discharged as paint residues.

TABLE 3-6

Sources and Estimates of United States Atmospheric Chromium Emissions*

Source Category	Chromium Emissions, Metric Tons/Year
Chrome Ore Refining	3
Ferrochromium Production	43
Chromium Chemicals Production	450-900
Refractory Production	90
Sewage Sludge Incineration	25 30
Steel Production	2870
Utility Cooling Towers	5
Cement Production	16
Combustion of Coal and Oil	
boilers	737
process heaters	556
Total	4825-5275

*Source: Radian Corporation, 1984

TABLE 3-7

Regional Distribution of Principal Chromium Emissions[a]

EPA Region/States	Annual Chromium Emissions From Sources in this Region, metric tons (Mg)[b]	Percent of Total U.S. Chromium Emissions
I/CT,ME,MA,NH,RI,VT	103	0.6
II/NJ,NY,PR,VI	3,140	19.0
III/DE,MD,PA,VA,WV,DC	2,800	17.3
IV/AL,FL,GA,KY,MS,NC,SC,TN	3,000	18.5
V/IL,IN,MI,MN,OH,WI	4,830	29.0
VI/AR,LA,NM,OK,TX	74	0.5
VII/IA,KS,MO,NB	177	1.1
VIII/CO,MT,ND,SD,UT,WY	107	0.7
IX/AZ,CA,NV,HA	174	1.1
X/AK,ID,OR,WA	898	5.4
TOTAL	15,300	93.2

[a] Source: GCA Corporation, 1973

[b] Sources include ferrochrome production, refractory production, cement production, chrome steel production, and coal and oil combustion.

Solid waste streams containing Cr(VI) constitute the primary problem area involving chromium solid wastes (Hartford, 1979). Wastes resulting from the roasting and leaching steps in the chromate manufacturing process traditionally contain residual Cr(VI). If landfilled, the residual Cr(VI) can slowly leach into surrounding waters via desorption and disproportionation (Hartford, 1979). An estimate of the total amount of chromium released into soil and groundwater as a result of the leaching of chromium-containing solid wastes is not available.

3.3. ENVIRONMENTAL FATE AND TRANSPORT

3.3.1. Air. Little information exists in the literature regarding the nature of the chemical species present in the atmosphere away from obvious sources of pollution. Under normal conditions, Cr(III) and Cr(0) are relatively unreactive in the atmosphere (Towill et al., 1978). Cr(VI) in air may react with particulate matter or gaseous pollutants to form Cr(III) (NAS, 1974). However, these atmospheric reactions have not been extensively studied.

Low concentrations of chromium enter the atmosphere as a result of industrial activities and soil-derived aerosols (Towill et al., 1978). Chromium is removed from air through wet and dry depositions. The total yearly deposition of chromium in urban areas may vary from 0.12 $\mu g/m^2$ to 3 $\mu g/m^2$ (Towill et al., 1978). In general, urban areas have higher total deposition than rural areas. Chromium concentration in a wet deposition may vary from 0.004 to 0.060 $\mu g/m\ell$ and 0.0006 to 0.034 $\mu g/\ell$ for urban and rural areas, respectively (Towill et al., 1978). The precipitated chromium from the air enters the surface water or soil.

Chromium particles of aerodynamic equivalent diameter <20 μm may remain airborne for long periods and may be transported great distances by wind currents and diffusion forces (Sehmel and Hodgson, 1976). Therefore, atmospheric conditions play an important role in determining the chromium concentration around emission sites; however, no data relating atmospheric chromium content to atmospheric or meteorological conditions could be found in the literature.

3.3.2. Water and Sediments. Surface runoff, deposition from air, and release of municipal and industrial wastewaters are the sources of chromium in surface waters. Chromium may be transported in five forms (see Table 3-8) in surface waters.

It can be seen from Table 3-8 that most of the chromium in surface waters may be present in particulate form as sediment. Some of the particulate chromium would remain as suspended matter and ultimately be deposited in sediments. DeGroot and Allersma (1973) found a chromium ratio in water to suspended matter to be 1 to 2.3 for the Rhine River. In the heavily polluted Qishon-Gadura River in Israel, chromium concentrations in water were <10 ppb, while sediment contained from 220 to 610 ppm chromium (Towill et al., 1978).

The exact chemical forms of chromium in surface waters are not well defined. Although most of the soluble chromium in surface water may be present as Cr(VI) (Towill et al., 1978), a small amount may be present as Cr(III) organic complexes (DeGroot and Allersma, 1978; Fukai, 1967). Schroeder and Lee (1975) studied the transformation between Cr(III) and Cr(VI) in natural waters. They found that only 3% of Cr(III) was oxidized by O_2 in 30 days at ambient temperature. Cr(VI) is the major stable form of chromium in seawater (Fukai, 1967); however, Cr(VI) may be reduced to Cr(III) by organic matters present in water and may eventually deposit in sediments. Lu and Chen (1976) found that chromium was not significantly released from sediments into seawater under either oxidizing or reducing conditions. Eisenreich (1982), however, noted that in some waterbodies, such as

TABLE 3-8

Five Forms of Chromium Transported in the Yukon and Amazon Rivers*

Physical Form	Percent Present In Amazon River	Percent Present In Yukon River
In solution and organic complexes	10.4	12.6
Adsorbed	3.5	2.3
Precipitated and co-precipitated	2.9	7.2
In organic solids	7.6	13.2
In sediments	75.6	64.5

*Source: Towill et al., 1978

Lake Superior, chromium occurred in trace amounts from in-lake processes. He estimated an atmospheric chromium flux of 0.9 $\mu g/m^2$/day on the surface film.

3.3.3. Soil. Most soil chromium is in mineral, absorbed, or precipitated form. Chromium probably occurs as the insoluble Cr(III) oxide ($Cr_2O_3 \cdot nH_2O$) in soil, as the organic matter in soil is expected to reduce any soluble chromate to insoluble Cr_2O_3. Chromium in soil can be transported to the atmosphere by way of aerosol formation (John et al., 1973; Zoller et al., 1974). Chromium is also transported from soil through runoff and leaching of water. Runoff could remove both chromium ions and bulk precipitates of chromium with final deposition on either a different land area or a water body. In addition, flooding of soils and the subsequent anaerobic decomposition of plant matters may increase dissolution of Cr(III) oxides in the soil (Towill et al., 1978).

3.4. LEVELS OF CHROMIUM IN VARIOUS MEDIA

3.4.1. Ambient Air. Background concentrations of chromium in various media have been reported by Cary (1982). Citing the work of Maenhaut and Zoller (1977), he noted chromium concentrations at the South Pole were approximately 5 pg/m^3 (0.005 ng/m^3). He noted further that Duce and Zoller (1975) found that chromium levels over the Atlantic Ocean ranged from 0.007 to 1.1 ng/m^3. The authors believed that this trace amount of chromium originated from a crustal source.

The chemical form of chromium in air depends on the source of emission. The majority of chromium in the atmosphere, originating from such sources as metallurgical production, coal and oil combustion and cement production is usually in the Cr(III) or Cr(O) state. Chrome production, chrome plating, and cooling tower drifts are primary examples of the sources of Cr(VI) in the atmosphere (Towill et al., 1978). The mass median diameter of chromium in air particulate matter is in the range of 1.5 to 1.9 μm (Cawse, 1974; Lee and von Lehmden, 1973). Chromate salts are often used in the cooling tower water as a corrosion inhibitor. Therefore, cooling tower drift consisting of water droplets formed mechanically within the towers and carried by wind into the surrounding area may be a source of high Cr(VI) concentrations in air. Air concentrations of chromium near a cooling tower at the Oak Ridge Gaseous Diffusion Plant, Oak Ridge, Tennessee, were about 50 ng/m^3 from distances up to 660 feet (200 m) from the tower (Alkezweeny et al., 1975). Hourly chromium deposition was about 1 mg/m^2 at 100 feet (30 m) and about 0.01 mg/m^2 at 330 feet (1000 m) from the tower. Therefore, substantial amounts of chromium may be present in the respirable particulate fraction and can be deposited in the respiratory tract.

The concentrations of total chromium measured in the ambient air of many urban and nonurban areas of the United States during 1977 to 1980 are given in Table 3-9. The data in Table 3-9 were obtained from the U.S. EPA's National Aerometric Data Bank, which is maintained by the Agency's Monitoring and Data Analysis Division (MDAD) at Research Triangle Park, North Carolina. None of the data in Table 3-9 have been previously published. The ambient chromium data have been collected by monitoring networks operated by various State and local air pollution control agencies as required by the Clean Air Act. After passing editorial and validation checks which are performed by EPA regional offices, the data are forwarded to MDAD for incorporation into the National Aerometric Data Bank.

During the 1977-1980 period, the mean chromium concentrations measured in the United States (given in Table 3-9) ranged from 0.0052 μg/m^3 (24-hour average

TABLE 3-9

Total Chromium Concentrations Measured in the Ambient Air of Selected Sites in the United States During 1977-1980[a]

Site	Year	Total Chromium Concentration, $\mu g/m^3$ Arithmetic Mean[b]	Maximum Observed Value[c]
Grand Canyon, National Park, AZ[d]	1977	0.0058	0.0134
Los Angeles, CA	1977	0.0188	0.0666
Waterbury, CT	1978	0.0342	0.2178
	1979	0.0326	0.1396
Atlanta, GA	1977	0.0089	0.0441
	1980	0.0062	0.0194
Hawaii County, HI[d]	1977	0.0063	0.0216
Kansas City, KS	1977	0.0167	0.0413
	1978	0.0276	0.0724
	1980	0.0191	0.0358
Iberville Parish, LA	1977	0.0063	0.0159
	1978	0.0059	0.0128
	1980	0.0052	0.0052
Acadia National Park, ME[c,d]	1977	0.0052	0.0052
Baltimore, MD	1977	0.1568	0.2470[e]
	1979	0.0935	0.4589
Worcester, MA	1977	0.0063	0.0167
	1978	0.0099	0.0239
	1979	0.0067	0.0166
Bayonne, NJ	1977	0.0105	0.0253
	1978	0.0149	0.0324
	1980	0.0123	0.0508
Newark, NJ	1978	0.0181	0.0301
	1979	0.0129	0.0333
	1980	0.0091	0.0369
Niagara Falls, NY	1979	0.0389	0.5590
	1980	0.0144	0.0603

TABLE 3-9 (cont.)

		Total Chromium Concentration, µg/m^3	
Site	Year	Arithmetic Mean[b]	Maximum Observed Value[c]
Akron, OH	1977	0.0126	0.0610
	1978	0.0188	0.0528
	1979	0.0166	0.0389
	1980	0.0204	0.0710
Cincinnati, OH	1977	0.0083	0.0377
	1978	0.0116	0.0294
	1979	0.0451	0.4316
	1980	0.0150	0.0718
Steubenville, OH	1978	0.0517	0.2602
	1979	0.1212	0.6839
Black Hills National Forest, SD[c]	1978	0.0090	0.0295
Chattanooga, TN	1977	0.0122	0.0453
	1978	0.0140	0.0463
	1979	0.0112	0.0760
	1980	0.0150	0.0705
Norfolk, VA	1977	0.0067	0.0152
	1978	0.0069	0.0158
	1979	0.0083	0.0291
	1980	0.0119	0.1456
Tacoma, WA	1977	0.0099	0.0330
	1978	0.0249	0.1425
	1980	0.0104	0.0283

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[a] Source: Unpublished data in the National Aerometric Data Bank maintained by the Monitoring and Data Analysis Division of EPA, Research Triangle Park, NC.

[b] Values represent annual average.

[c] Values represent maximum 24 hour averages.

[d] Background sites; all other sites are determined to be populated urban areas.

[e] Corrected from Maryland State Yearly Air Quality Data Report, Baltimore MD, March, 1978.

background level) to 0.1568 $\mu g/m^3$ (urban annual average). The highest maximum 24-hour average of 0.6839 $\mu g/m^3$ was recorded in Steubenville, OH in 1979. For the sites with >2 years worth of data, no discernible upward or downward concentration trends are evident. For example, in Newark, New Jersey, the mean chromium concentration dropped from 0.0181 $\mu g/m^3$ in 1978 to 0.0129 $\mu g/m^3$ in 1979 and to 0.0091 $\mu g/m^3$ in 1980. However, in Norfolk, Virginia, over the same period the chromium levels rose from 0.0069 $\mu g/m^3$ in 1978 to 0.0083 $\mu g/m^3$ in 1979 and to 0.0119 mg/m^3 in 1980. In Akron, Ohio, the mean chromium concentration in 1978 was determined to be 0.0188 $\mu g/m^3$. In 1979, the concentration in Akron dropped to 0.0116 $\mu g/m^3$ but in 1980 it rose again to 0.0204 $\mu g/m^3$. The mean chromium concentrations in nonurban, background areas such as national parks ranged from 0.0052 $\mu g/m^3$ to 0.0090 $\mu g/m^3$ over the 1977 to 1980 period.

Some source categories emit trivalent chromium, some emit hexavalent chromium and others emit a combination of the two. Sources likely to be trivalent emitters are refining, cement production and coal and combustion. Hexavalent sources include chrome plating and cooling towers. Those that emit both forms include chromium chemicals production, refractory production, steel manufacturing, and sewage sludge and municipal refuse incineration. The relative proportions of each form emitted are unknown at this time. Maximum annual average concentrations predicted, based on dispersion modeling, with 20 km of these source categories range from 0.01 $\mu g/m^3$ for refractory production.

3.4.2. Aquatic Media. Naturally occurring chromium concentrations in water arise from the weathering of minerals, soluble organic chromium, sediment load and precipitation (Cary, 1982). Of 170 lakes sampled in the Sierra mountains in California, only two contained up to 5 $\mu g/\ell$ (ppb) chromium; the mean pH was 6.0 (Cary, 1982). Both the Amazon and Yukon rivers, which are considered to represent unpolluted watershed systems, reportedly contained 2.0 and 2.3 $\mu g/\ell$

(ppb) chromium, respectively (Gibbs, 1977). These background freshwater chromium levels compare well with estimates given by Bowen (1979) (median of 1 μg/ℓ (ppb) chromium within a range of 0.1 to 6 μg/ℓ (ppb)). Morevoer, Cary (1982) notes that over 95% of the stream and river water sampled in Canada for chromium contained less that 10 μg/ℓ (ppb). The chromium levels detected in a few surface waters and groundwaters are presented in Table 3-10. The amounts of chromium found in these waters are usually related by the authors to anthropogenic input. For example, it has been shown by Kopp and Kroner (1967) that water from Lake Michigan near industrial discharge points contained a higher level of chromium than lake water contaminated with lesser industrial input (5 to 19 ppb, compared to 2 to 4 ppb).

The valence of chromium in surface water can be either VI or III. Although Cr(VI) is the more stable species in seawater, Fukai (1967) provided data to show that both Cr(III) and Cr(VI) were present. Surface seawater contained Cr(III) and Cr(VI) in the range of 0.02 to 0.14 ppb and 0.28 to 0.36 ppb, respectively, while seawater at depths of 5, 500, and 1000 m contained about the same level (0.2 ppb) of Cr(III) and Cr(VI). Cranston and Murphy (1978) found that the ratios increased at depths greater than 100 m. In areas of the Pacific Ocean, chromium levels averaged 0.12 μg/ℓ (ppb). Above 100 m, 83% occurred as Cr(VI); below 100 m chromium averaged 0.16 μg/ℓ (ppb), and CR(VI) accounted for approximately 90%.

In a survey of 14 groundwater and 69 surface water supplies in 83 United States cities in Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin, the chromium level in the raw waters used for drinking waters were found to range between <5.0 and 17.0 ppb (see Table 3-11) (U.S. EPA, 1975). Groundwater contamination of 220 μg/ℓ (ppb) Cr(VI) was reported by Robertson (1975) in ground water of Paradise Valley, AZ.

TABLE 3-10

Chromium Levels in a Few Surface Waters and Groundwaters[a]

Source	Frequency of Detection %	Conc. (ppb or µg/ℓ) in Samples with Detectable Chromium Level: Average	Range
Lake Tahoe	NR	<0.62	<0.07 to <0.91
Colorado River	12	NR	10 to 30
Columbia River	87	NR	1 to 10
Mississippi River	23	NR	3 to 20
Missouri River	10	NR	8 to 10
Ohio River	20	NR	4 to 16
U.S. surface waters	25	<1	<1 to 19
U.S. surface waters	25	9.7	1 to 112
Natural water, Oak Ridge, TN	NR	NR	50 to 120
Water near cooling tower, Oak Ridge, TN	NR	NR	2500 to 2790
Uncontaminated stream, NY	NR	<10	NR
Contaminated stream, NY	NR	1250	NR
Uncontaminated well, NY	NR	<10	NR
Contaminated well, NY	NR	6000	NR
Illinois River	NR	21	5 to 38
Spring water, CA	6	NR	0 to 21
Well water, CA	5	NR	0 to 13
Stream water, CA	0	NR	NR
Seawater, CA	0	NR	NR

[a] Source: Towill et al., 1978

NR = Not recorded

TABLE 3-11

Chromium Concentrations in U.S. Drinking Waters[a]

Water	Concentration, μg/ℓ or ppb	
	Median	Range
Tap water, Dallas, TX	4[b]	1 to 20
100 largest cities, U.S. (1962)	0.4[c]	0.2 to 35
380 finished waters, U.S. (1962-1967)	7.5[b]	1 to 29
3834 tap waters, U.S. (1974-1975)[d]	1.8[b]	0.4 to 8[g]
83 Midwestern cities, U.S.[e]	NR	<5.0 to 17.0
115 Canadian municipalities (1976-1977)[f]	≤2.0	≤2.0 to 4.1

[a] Source: NAS, 1977

[b] Average value; sampling date unavailable

[c] Median value

[d] Greathouse and Craun, 1978

[e] U.S. EPA, 1975; sampling date unavailable

[f] Méranger et al., 1981

[g] 28% of areas had detectable levels

NR = Not recorded

The chromium concentration in various United States drinking water supplies is presented in Table 3-11. In a survey of 2595 water samples from 969 water supplies in the United States, only four samples showed chromium levels above the detection limit of 50 ppb (McCabe et al., 1970). The maximum chromium concentration in water detected in this survey was 80 ppb.

In a more recent survey (1974 to 1975) with an analytical method of better sensitivity, 3834 tap waters from 35 geographical locations representative of the U.S. population were monitored for metal content (Greathouse and Craun, 1978). The detection limit for Cr in this survey was 0.1 ppb. The results of this survey, presented in Table 3-11, also indicated that 28% of the area surveyed had Cr levels above the detection limit. It should be mentioned that the mean value of Cr in this study may be a little higher than reported since the tap waters were not adequately flushed before collection.

3.4.3. Aquatic Suspended Materials and Sediments. The concentration of chromium in suspended materials in several United States rivers was found to range between 37 and 460 ppm on a dry weight basis (Turekian and Scott, 1967). Chen et al. (1974) determined the concentration in dry season suspended silts of Southern California waters to be ≃500 ppm in "natural" areas and 2000 ppm in urbanized areas.

Chromium concentrations determined for a variety of bottom sediments are shown in Table 3-12. For the areas in the United States sampled, sediment chromium levels ranged from about 1 to 450 ppm. An examination of Table 3-12 shows that the chromium concentration in sediments from several Wisconsin lakes and Southern Lake Michigan does not significantly decrease with depth. A similar finding concerning sediment chromium content was made by Bruland et al. (1974) upon the analysis of chromium levels in sediments of different depths from the

TABLE 3-12

Concentration of Chromium in Sediments*

Area	Chromium Concentration (ppm) Median	Range
Delaware Bay	NR	33 to 447
New York City Bight:		
Background	106	2 to 310
Sludge dumping area	105	50 to 209
Puget Sound	NR	43 to 154
Houston ship channel, TX	NR	39 to 254
Neches River, TX	NR	8 to 288
Sabine River (low in industrial activity) TX-LA Border	NR	41 to 89
Southern Lake Michigan:		
surface sediments	77	35 to 165
sediments from >15 to 100 cm depth	52	32 to 68
estimated background	NR	20 to 40
Illinois River	17	2 to 87
Non-industrial stream, IL	6	3 to 7
Buzzard Bay, MA	33	NR
Wisconsin Lakes:		
surface sediment	NR	1 to 49
sediment from >50 cm depth	NR	0.8 to 35

*Source: Towill et al., 1978
NR = Not recorded

Southern California basin. These studies of sediment chromium content versus depth appear to indicate that natural background chromium levels contribute heavily to the chromium levels found in surface sediments.

The concentration of chromium in an incinerated sewage sludge ash was determined to be 5280 μg/g (ppm). The concentrations of metals in ash residue after incineration is ≈4 times those present in dried sludge (Fraser and Lum, 1983). Therefore, based on this one analysis, sewage sludges may contain high concentrations of chromium.

3.4.4. Soil. The concentration of chromium in soil varies in accordance with soil origin. Soils derived from nonserpentine areas can contain from traces to 300 ppm chromium. Soils derived from serpentine areas can contain up to 2% by weight of chromium. The chromium concentrations in selected soils from various parts of the U.S. are shown in Table 3-13. Mean chromium levels in Canadian soils were 43 ppm (McKeague and Wolynetz, (1980). Most chromium in soils is apparently insoluble. Extraction of soils with 2.5% acetic acid, ammonium acetate at pH 4.8, and even with 0.1 N HCl have shown that only 0.01 to 4% of the total soil chromium is extractable (Towill et al., 1978). Generally, chromium concentrations in soils correlate well with chromium concentrations in parent rock (Cary, 1982).

3.4.5. Food. The chromium content of a variety of foods is presented in Table 3-14. The values given in Table 3-14 represent the average of several food items in each category. It can be seen from this table that the chromium concentrations in different categories of food determined by Schroeder et al. (1962) were lower than the values determined by other investigators. It is not known whether the observed discrepancies are due to geographical and seasonal

TABLE 3-13

Chromium Content in Selected United States' Soils*

Location	Soil Characteristic	Chromium content ppm or μg/g Range	Median
Pennsylvania	agricultural surface and subsoil	NR	14
Peninsular Florida	surface and subsoil	<1 to 1000	50
Florida	surface and subsoil	<1 to 500	NR
Missouri	on and off road soil	NR	71
New Jersey	various soils	29 to 75	NR
Michigan	various surface soils	3.2 to 17.6	NR

*Source: Towill et al., 1978
NR = Not recorded

TABLE 3-14

Chromium Content in Various U.S. Foods

Sample	Mean Concentration (ppm or μg/g)	Reference
Fresh vegetables	0.14	Thomas et al., 1974
Fresh vegetables	0.03 to 0.05	Schroeder et al., 1962
Fresh vegetables	0.14	Toepfer et al., 1973
Frozen vegetables	0.23	Thomas et al., 1974
Canned vegetables	0.23	Thomas et al., 1974
Fresh fruits	0.09	Toepfer et al., 1973
Fresh fruits	0.19	Thomas et al., 1974
Fruits	0.02	Schroeder et al., 1962
Canned fruits	0.51	Thomas et al., 1974
Dairy products	0.10	Schroeder et al., 1962
Whole fish	0.05 to 0.08	Okuno et al., 1978
Meat and fish	0.23	Toepfer et al., 1973
Meat and fish	0.11	Schroeder et al., 1962
Sea foods	0.12	Zook et al., 1976
Sea foods	0.47	Méranger and Somers, 1968
Grains and cereals	0.04	Schroeder et al., 1962
Grains and cereals	0.22	Toepfer et al., 1973
Fruit juices	0.09	Méranger, 1970

variations in trace element content of foods or due to errors in analytical determinations.

The chromium content in acidic foods is often higher than other categories of foods. The values of Cr content in a few commercial acidic foods which had been in contact with stainless steel surfaces during harvesting, processing, or preparation for market are shown in Table 3-15 (Stoewsand et al., 1979). Jennings and Howard (1980) reported slightly higher levels of Cr in British commercial alcoholic beverages than the Cr content in U.S. wines as given in Table 3-15. The chromium contents in wines, beers, and spirits were reported to be 0.45, 0.30, and 0.135 mg/ℓ (ppm), respectively. However, it is difficult to assess the daily chromium intake in the United States from the Cr content in individual foods. The chromium contents in a selected diet composite were determined by Kumpulainen et al. (1979). This study is the most recent diet study conducted by FDA-USDA (personal communication with Dr. W.R. Wolf, USDA). The chromium intake from typical American diets containing 43% fat was determined to be 62 ± 28 μg/day. The corresponding intake from typical American diets containing 25% fat was determined to be 89 ± 56 μg/day.

3.4.5.1. BIOCONCENTRATION IN FOOD CHAINS -- Several authors have found that chromium concentrations decrease in higher trophic level organisms in aquatic ecosystems (Towill et al., 1978). For example, Mathis and Cummings (1973) detected ≈10 ppm chromium in worms, ≈5 ppm in clams, ≈1.2 ppm in omnivorous fish, and ≈1 ppm in carnivorous fish. Lack of assimilation of chromium is probably the major reason that the organisms of the higher trophic levels contain lesser amounts of chromium.

A bioconcentration factor (BCF) is the ratio of the concentration of a chemical in aquatic species to the concentration in the water in which they live.

TABLE 3-15

Concentration of Chromium in a Few Commercial Grade Acidic Foods[a]

Commodity	Container	Sample pH	Cr Concentration, ppm or µg/g (wet wt.)
Red cabbage	glass	--	2.6
Red cabbage brine	glass	3.4	10.3
Sauerkraut	can	--	0.3
Sauerkraut brine	can	3.5	0.3
Sauerkraut	flexible pouch	--	0.2
Sauerkraut brine	flexible pouch	3.5	0.2
Different brand of honey	glass	3.5 to 3.7	0.04 to 0.18
Vinegar	bulk	2.8	0.01
Hard cider	bulk[b]	3.5	0.004
Cheese whey	bulk	4.8	0.01
Wine, Catawba	lastiglass (1 year)	3.1	0.02
Wine, red concord	redwood (8 months)	3.2	0.07
Wine, red concord	stainless steel (7 months)	3.2	0.02

[a] Source: Stoewsand et al., 1979

[b] Before acidification

An appropriate BCF can be used with data concerning food intake to calculate the amount of chromium which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals is similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980b) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

The BCF for Cr(VI) in fish muscle appears to be less than 1.0 (Buhler et al., 1977; Fremm and Stokes, 1962), but values of 125 and 192 were obtained for oyster and blue mussel, respectively (U.S. EPA, 1980c). For Cr(III), BCF values of 116, 153, and 86 were obtained with the American oyster (Shuster and Pringle, 1969), soft shell clam, and blue mussel (Cappuzzo and Sasner, 1977), respectively. It appears that the two valence states of chromium(III and VI) have about the same BCF values, and that the geometric mean of 130 can be used for bivalve molluscs. If the values of 0.5 (BCF for fish and mussels) and 130 (BCF for bivalve molluscs) are used with the consumption data, the weighted average bioconcentration factor for chromium in the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans can be calculated to be 16 on the basis of per capita consumption of 0.8 g/day and 5.7 g/day for bivalve molluscs, and fish and shellfish, respectively (U.S. EPA, 1980b).

3.4.6. Cigarettes. Chromium has been determined to be a component of cigarette tobacco. Tobaccos grown in the United States have been found to have a chromium content ranging from 0.24 to 6.3 mg/kg (ppm) (IARC, 1980).

3.5. INDICES OF EXPOSURE

Past exposure to low levels of chromium may be associated with higher than normal levels of chromium in the blood, urine and hair. In hair samples, the relationships are tenuous in young children and women, as a result of variation in chromium levels related to age and pregnancy (Creason et al., 1975). In blood and urine, marked variations have been reported in the linearity between exposure levels and the levels in body fluids as a result of sequestering and release of chromium from body depots.

3.5.1. Chromium in Blood. Chromium is absorbed through both the respiratory and gastrointestinal tracts (U.S. EPA, 1978). In the respiratory tract, water and serum soluble chromates are absorbed into the blood system, whereas insoluble Cr(III) particles and the inert oxides and hydroxides of Cr(III) remain in lung tissue (U.S. EPA, 1978). In the blood stream, chromium compounds are bound by proteins (Gray and Sterling, 1950). It has been shown that ionic Cr(VI) (injected intravenously) passes through the membrane of red blood cells and binds to the globin moiety of hemoglobin. Once inside the erythrocyte, Cr(VI) compounds are rapidly reduced to Cr(III) and are unable to pass through the cell membrane (Aaseth et al., 1982; Yamaguchi et al., 1983). In healthy red cells, Cr(III) is partially bound to hemoglobin and partially to small molecular weight substances.

Chromium disappears quickly from the blood and is taken up by other tissues in the body, where it is concentrated much more heavily (by a factor of 10 to 100) than in the blood. Therefore, blood levels of chromium may not be a usable indicator of chromium nutritional status (Mertz, 1969; Mertz and Roginski, 1971).

A wide range of values for chromium content in blood has been reported. Schroeder et al. (1962) reported chromium levels in serum of 0.52 and 0.17 ppm, whereas Doisy et al. (1969, 1971) found a chromium concentration of 2 ppb in serum. Other chromium values reported have ranged from 0.11 to 55 ppb in human plasma, and from 5 to 54 ppb in red blood cells (Underwood, 1971). Imbus et al. (1963), working with United States subjects, found blood chromium levels ranging from 13 to 55 ppb with a median of 27 ppb, while Hamilton et al. (1973), studying subjects from the United Kingdom, reported a blood level of 70 ppb chromium.

However, researchers have discovered, through the use of new technology in flameless AAS analyses, that the amount of chromium in normal blood and urine was an order of magnitude lower than previous measurements had shown. It was considered by Guthrie et al. (1978), Kayne et al. (1978) and Anderson (1981) that measurements made before 1978 are probably high as the result of inadequate background correction for non-atomic absorption. Thus, measurements of absolute values of chromium in normal body fluids made before 1978 are unreliable (Toxic Material News, 1982), although they were useful as pioneering attempts to elucidate chromium metabolism.

Kayne et al. (1978) used flameless AAS with a tungsten halogen light source for background correction to determine the serum chromium levels in 8 normal male subjects. The tungsten halogen light greatly improved the background correction in the near UV region where chromium is detected as compared to the standard D_2 light source. With the elimination of non-atomic absorption, the mean level of serum chromium was determined to be 0.14 $\mu g/\ell$ (ppb). These results were in agreement with those of Versieck et al. (1978) in which serum chromium was determined by neutron activation analysis. Serum obtained from 20 healthy subjects (duplicate samples from 14 subjects) had a range of chromium levels from 0.0382 to 0.351 $\mu g/\ell$ (ppb) with a mean value of 0.16 $\mu g/\ell$ (ppb). Using this data, the authors concluded that normal human chromium levels in serum are in the sub-ppb range. Plasma or whole blood chromium levels have ranged from 4-70 ppb, with a mean value of 30 ppb (total chromium) (Lin, 1983).

3.5.2. Chromium in Urine. A wide range of values for chromium content in urine has been reported. Hambidge (1971) reported chromium levels in urine of 8.4 ppb for adults and 5.5 ppb for children over a 24-hour period. Imbus et al. (1963) reported median urinary concentrations of chromium for adult males of 3.77 μg/ℓ (ppb). Renal excretion is the major pathway of chromium elimination, with ≥80% of injected chromium excreted in this manner (Mertz, 1969).

As discussed with chromium levels in serum, difficulties in determining the low levels of chromium in urine were not resolved until 1978, and presently, normal human levels of chromium are considered to be in the sub-ppb range (Anderson, 1981). Using flameless AAS with background correction by either a tungsten halogen lamp or a continuum source, echelle, wavelength modulated AA system (CEW-AA), normal human urinary chromium levels were determined to be >1 μg/ℓ (ppb) (Guthrie et al., 1978), >0.9 μg/ℓ (ppb) for most of 66 samples (Kayne et al., 1978), and between 0.05 to 0.58 μg/ℓ (ppb) for 48 males and 28 females (Anderson et al., 1982). Veillon et al. (1979) obtained excellent agreement between chromium determinations of pooled urine samples using CEWM-AA and chromium determinations using stable isotope dilution methods measured by GC/MS. The mean values for the respective methods were 0.34 ± 0.1 and 0.32 ± 0.02 μg/ℓ (ppb). Increases in urinary chromium in humans receiving a daily supplement of 200 μg Cr as $CrCl_3$ ranged from mean levels of 0.2 μg/ℓ (ppb) prior to treatment to 1.02 and 1.13 μg/ℓ (ppb) after 2 and 3 months. Although Anderson (1981) cautions against accepting absolute values for chromium from earlier studies, comparisons and trends determined in a given study may be valid.

Franchini et al. (1975) and Borghetti et al. (1977) reporting about workers exposed to chromium in the chromium-plating industries showed that urinary excretion and renal clearance of diffusible chromium are biological indices to evaluate the degree of current exposure and the body burden of the compound.

Franchini et al. (1978) confirmed their earlier results with an experimental investigation using rats.

Other authors have demonstrated a close relationship between the amount of Cr(VI) in the air and urinary excretion (Gylseth et al., 1977) or urinary excretion of the metal corrected for creatinine (Tola et al., 1977). Gylseth et al. (1977) reported in an abstract that welders exposed to a concentration of 0.05 mg/m^3 (measured as chromium) had a urinary chromium concentration of ≈40 μg/ℓ, measured after work. Sjogren et al. (1983) showed a linear relationship between worker exposure to stainless steel welding fumes and urinary chromium levels.

Krishna et al. (1976) studied 30 chrome workers who had nasal perforation. The atmospheric concentration of chrome ranged from 0.21 to 0.80 mg/m^3. Urine samples from the workers were collected at the beginning of the day's shift and again at the end of the day's shift. Before exposure, eight workers had a concentration of chrome in the urine of $\geq$0.20 μg/ℓ (ppm), whereas after exposure, 20 workers had such values. In an unexposed control group, there was no change in the urine chrome values. While all the workers tested had nasal perforation, 66% of them (20 of 30) had a urinary chrome concentration of $\geq$0.20 μg/mℓ (ppm).

Mutti et al. (1979) studied 22 welders who worked with high chromium alloyed electrodes. The concentration of the breathing zone levels of chromium, determined during the 1-month exposure monitoring period, ranged from 0.017 to 1.000 mg/m^3 for total chromium, and from 0.002 to 0.350 mg/m^3 as hydrosoluble chromium. Urine samples from the workers were collected at the beginning and at the end of the experiment. These results suggest that the urinary concentration of chromium at the end of a working period is affected by recent exposure to the compound. At the same airborne concentration, the greater chromium body burden is associated with greater excretion levels. Even after a week following the last exposure, urinary chromium levels provide useful indications on body burden.

Tandon et al. (1977) have reported urinary excretion of chromium among electroplaters and polishers in an industrial setting. A total of 12 subjects were examined. The range in duration of exposure to chromium in electroplating processes ranged from 2 to 20 years (mean duration for 12 workers = 11.1 years). Chromium levels in workers' urine samples taken before starting work ranged from 91 to 1116 μg/ℓ (mean value = 326.5 μg/ℓ (ppb)). Urinary chromium levels did not necessarily correlate to duration of exposure, but a slight trend was indicated. Subjective complaints included coughing, breathing difficulty, dermal itching, depression, indigestion, body ache, and edema of the lower limbs. Mean urinary chromium level in appropriate controls was reported to be 38.1 μg/ℓ (ppb) (range: 0 to 78 μg/ℓ). Subjective complaints did not appear to correlate either with urinary chromium levels or with duration of exposure. Urine samples collected at the end of the work day, however, would perhaps have provided a better correlation between exposure and complaints of illness.

3.5.3. Chromium in Human Hair. Schroeder and Nason (1969) reported a mean chromium concentration of 0.69 ± 0.063 ppm for women. Hambidge et al. (1972) measured chromium concentrations at various distances from the hair root. They reported that variation in the concentrations were due to past fluctuations in chromium nutritional status. Hambidge and Rodgerson (1969) reported higher levels of chromium in the hair of nonpregnant women (0.2 to 2.81 ppm) than in the hair of pregnant women (0.04 to 1.14 ppm). However, a later study by Hambidge and Droegnueller (1974) found changes in hair chromium levels due to pregnancy not to be statistically significant. Hambidge and Rodgerson (1969) reported that hair chromium levels in 3- to 8-month-old infants were significantly higher than in those of 2- to 3-year-old children. Chromium is obtained through breast milk during nursing. By the second year of life, mean chromium levels in hair approached values present in older humans.

3.6. SUMMARY

Chromium is a metallic element which, when found in nature, is a stable mixture of four separate isotopes. Inorganic chromium compounds occur in valence states ranging from -2 to +6; however, in the environment the Cr(III) and Cr(VI) states are the most stable. Chemically, the Cr(III) state is the most stable and important form of inorganic chromium complexes. Cr(VI) compounds comprise the most commercially important form of chromium, and they also appear to be the most significant chromium compounds from an environmental standpoint. Because Cr(VI) is readily reduced in the presence of organic material, it is rarely found in nature apart from deposition by anthropogenic sources.

Although chromite ore is not currently mined in the United States, several chromium chemicals are domestically produced from imported ores. Sodium chromate, sodium dichromate, and chromic acid are three of the more important commercial chromium compounds produced in the United States. Metallurgical uses constitute about 60% of the largest market demand for chromium. Chemical uses are the second largest consumption sector at 21%, followed by refractory uses at 18%.

Chromium emissions are released into the air, water, and land environments from a variety of industrial source categories including fossil fuel combustion, cement production, incineration, cooling towers, refractory production, leather tanneries, steel and alloy production, electroplating, and chromite ore refining. The largest chromium emission sources to the air are coal and oil combustion, chromium chemicals production, refractory plants, and steel and alloy plants. Principal sources of chromium in water systems include electroplating operations, leather tanneries, and textile manufacturing operations. Significant sources of chromium-containing solid wastes that are land disposed include chromite ore refining operations and chromium chemical production plants.

Recent monitoring of the air in many urban and rural areas of the country has shown annual average chromium concentrations to be in the range of 0.0052 to 0.1568 µg/m^3; in remote parts of the world, concentrations as low as 0.005 ng/m^3 have been reported. The maximum concentration determined during any one 24-hour measurement was about 0.6839 µg/m^3. The chromium concentration in U.S. waters varies with the type of surrounding industrial sources and the type of underlying soils. An analysis of 3834 tap waters in representative U.S. cities showed a chromium concentration range of from 0.4 to 8 ppb. Chromium levels in soils vary with soil origin and the degree of contamination from anthropogenic chromium sources. Tests on domestic soils have shown chromium concentrations ranging from 1 to 1000 ppm, with the average concentration ranging from 14 to about 70 ppm.

4. SAMPLING AND ANALYSIS

Chromium occurs in trace amounts and throughout the environment and is an essential micronutrient for man. While numerous methods have been used to measure chromium in various media, only recent methods have provided the accuracy to measure this analytically troublesome element. Moreover, most of the more accurate methods measure elemental chromium; few provide usable information on the oxidation states for trace amounts.

The analysis of chromium in a certain medium usually involves three distinct steps, namely, sampling and storage, sample pretreatment, and analysis. These steps, and the media to which they apply, are discussed below.

4.1. SAMPLING AND STORAGE

4.1.1. Air.

4.1.1.1. AMBIENT AIR -- Dusts and fumes of chromium compounds in the ambient air are usually collected by high volume sampler at a flow rate of about 20 to 30 m^3 hr^{-1} (Demuynck et al., 1976). Typical filter media include cellulose, polyethylene, polystyrene, PVC, and glass-filter. The suitability of the filtering media primarily depends on their background impurity level, particle retention efficiency, and tendency to become clogged. Dams et al. (1972) evaluated different filter materials and concluded that polyethylene filters are most suitable for the collection of chromium particles in atmospheric air.

When size fractionation is required, multistage cascade impactors are used most often (Broekaert et al., 1982; Winchester et al., 1981; Kowakzyk et al., 1982). At a nominal sampling rate of 80 ℓ min^{-1}, chromium particles of aerodynamic diameter in the range of 0.04 to 25 μm have been separated by this method (Broekaert et al., 1982). The collection surfaces usually consist of polycarbonate films, accompanied by Nucleopore backup filters (Kowakzyk et al., 1982). However, according to Jervis et al. (1983), Nucleopore filters contain chromium impurities. Chromium found in aerosols from the burning of coal, and chromate from manufacturing plants, occur as small particles, less than 2 um and less than 0.4 um, respectively (Cary 1982).

Although no specific information is available, it is reasonable to assume that the filter paper protected from external contamination can be stored for an indefinite period prior to chromium analysis.

4.1.1.2. OCCUPATIONAL AIR -- Chromium in occupational air is collected in a way similar to ambient air. A known volume of air is drawn through a polyvinyl chloride (PVC) or cellulose filter. The sampling rate is maintained at 1.5 ℓ min^{-1} (NIOSH, 1977). However, it has been determined by Kneebone and Freiser (1975) that although the PVC filter can be stored for at least 10 days, cellulose filters cannot be stored for more than several hours without some loss of Cr(VI).

4.1.1.3. STATIONARY SOURCE -- The sampling of chromium from stationary sources, for example from the stack gasses of refuse incineration and fossil fuel burning facilities, can be done by collecting the sample isokinetically (Block and Dams, 1976; Greenberg et al., 1978). The sampling train typically consists of a copper probe, a rotameter, a manometer, and a pump with a capacity of 20 m^3 hr^{-1}. The diameter of the nozzle is adjusted to the stack gas velocity to achieve isokinetic sampling conditions (Block and Dams, 1976). Depending on gas temperatures, glass-fiber, Teflon-fiber, and Whatman 41 filters have been used (Block and Dams, 1976; Greenberg et al., 1978). However, the use of glass-fiber filters may result in a high blank value for chromium (Greenberg et al., 1978).

For studying distribution of particle size, the isokinetic sampling is typically done in combination with a multi-stage cascade impactor (e.g., Andersen cascade impactor) (Greenberg et al., 1978; Block and Dams, 1976). The different stages of the cascade impactor can be used to determine the cutoff aerodynamic diameters of the collected particles.

The same method used for storing the filters from ambient air samples can be used for the filters collected from the sampling of stationary sources.

4.1.2. Water.

4.1.2.1. DRINKING WATER -- To collect distributed water samples from household taps, the taps are typically run to waste at their maximum flow rate for 5 minutes to clear the lines of overnight standing water (Meranger et al., 1981). If suspended solids are suspected in the water, filtration is typically done on location by passing the water samples through a 0.45 μm Millipore membrane filter (Meranger et al., 1979). In order to get representative samples, some investigators (Greathouse and Craun, 1978) have collected monthly samples of finished water for a period of 1 year instead of one grab sample. The water samples are collected in clean linear polyethylene screw-cap collection bottles. Concentrated nitric acid (1 mℓ/100 mℓ water sample) is added to each bottle and they are filled to the brim to avoid any air space. The filled and capped bottles are transported in heavy plastic coolers containing gel-type freezer packs. Immediately upon receipt in the laboratory, samples should be refrigerated at 4°C (Meranger et al., 1981).

Recently, a novel method for preconcentration of trace metals in water samples has been proposed by Smits and Grieken (1981). In this method, a cylindrical plexiglass filtration unit consisting of a Nucleopore 0.4 μm pore-size membrane and a 2,2'-diaminodiethylamine (DEN)-cellulose filter has been used. The Nucleopore filter was used to separate the suspended particles in water and the DEN-cellulose filter allowed straightforward preconcentration of trace cations by a simple filtration step. The collection efficiency for Cr(III) by this method has been claimed to be 90-100%.

4.1.2.2. RAW AND SURFACE WATER -- The sample collection, preservation, transportation, and storage of raw and surface water samples are similar to those for drinking water samples (Cranston and Murray, 1978; Pankow et al., 1977). A more representative sample can be obtained by collecting several small samples from different parts of the water body than by collecting one large sample at a single point because of the inhomogeneity of the water body.

4.1.2.3. WASTEWATER -- The sample collection, preservation, transportation, and storage of wastewater samples are similar to those for other water samples. Grab samples (Larochelle and Johnson, 1978) are often collected but wherever a process change is suspected, a 24-hour composite sampling is the preferred or even necessary method.

4.1.3. Soil and Sediments. Grab samples are typically collected for the analysis of chromium in soil and sediment. In order to evaluate the chromium content in recent deposits, samples are collected from the upper few inches (2 to 3 inches) of sediment or soil (Pankow et al., 1977). The samples are usually stored in polyethylene bags or bottles (Iwata et al., 1981; Pankow et al., 1977).

The samples are sieved through nylon sieves (2 mm) to remove gravel and leaves (Iwata et al., 1981). The collected samples should be stored at 4°C or refrigerated during transportation and storage to minimize bacterial action (U.S. EPA, 1979).

4.1.4. Food. No specific information for sample collection and storage of food samples could be found in the literature. It is reasonable to assume that grab samples collected in polyethylene bags or bottles and refrigerated during transportation and storage should be an acceptable procedure for sample collection and storage.

4.1.5. Biological Samples. Blood samples are typically drawn from donors with either vacutainers or disposable syringes and aluminum needles. Heparin is used as the anticoagulant. Plasma samples can be obtained by centrifuging freshly drawn heparinized whole blood. They can be transported at 4°C in polyethylene tubes and frozen to -20°C during storage. Urine should be collected from donors in polyethylene bottles, acidified, and stored at 4°C (Davidson and Secrest, 1972). Other solid tissue samples can be collected in polyethylene bags and transported at 4°C. The tissue samples can be stored at -20°C. Lin (1982) noted sources of contamination can arise from steel needles used for blood drawing and from borosilicate glass containers which contain 1-10 μg/Cr/g glass. Moreover, in urine determinations utilizing atomic absorption, interferences can arise from absorption by NaCl or organic materials in the urine (Ping et al., 1983).

4.2. SAMPLE PRETREATMENT

Sample pretreatment is often required as a technique to release the metal from the sample matrix, and for concentration and separation from potential interferences. A few of the typical pretreatment methods have been discussed below. Generally, the pretreatment of samples is dictated by the subsequent method of analysis.

4.2.1. Wet and Dry Ashing. This pretreatment method is often used for chromium analysis in air particulate matter, biological samples, foods, soil, and sediment samples in combination with atomic absorption, atomic emission, spectrophotometric, and neutron activation analysis. In wet digestion or extraction methods, the sample is digested with an acid or a mixture of acids depending on the sample matrix. The composition and efficiency of commonly used methods are listed in Table 4-1. Acid mixtures which have been used include both HNO_3 and H_2SO_4 (NIOSH, 1977), HNO_3/HF (Pankow et al., 1977), H_2SO_4/H_2O_2 (Kumpulainen et al., 1979), HNO_3/H_2O_2 (Abu-Samra et al., 1975), $HClO_4/H_2O_2$ (Davidson and Secrest, 1972), $HNO_3/HClO_4$ (Gallorini et al., 1976), $HNO_3/H_2SO_4/HClO_4$ (Kuennen et al., 1982; Feldman et al., 1967) and HNO_3/H_2SO_4 (Bryson and Goodall, 1981). The two commonly used dry ashing procedures are graphite furnace ashing (Meranger et al., 1979; Slavin, 1981) and low-temperature oxygen plasma ashing (Kumpulainen et al., 1979). Some investigators also have used a combination of dry and wet ashing for the pretreatment of samples (Kumpulainen et al., 1979). Whichever procedure is used, a particular ashing method is always optimized to minimize matrix interference and maximize the chromium yield from the sample.

4.2.2. Precipitation. The direct precipitation of chromium from aqueous solution by such reagents as hydroxyquinoline and tannic acid is generally not suitable for environmental samples containing low chromium concentration. However, the method of co-precipitation of chromium has been successfully used in

TABLE 4-1

Composition and Efficiency of AA Extractant Solutions[a]

Efficiency[b]	Type and Volume (mℓ) of Acid Mixtures[c]				References
	Nitric	Hydrochloric	Sulfuric	Perchloric	
58.7	50 (2m)[d]				Day et al. (1975)
66.6		50 (2 m)[d]			Day et al. (1975)
62.7	50				Agemian and Chau (1976a)
67.9		50			Agemian and Chau (1976a)
65.8	25	25			Chiu and Hilborn (1979)
60.9	24	24	4		Chiu and Hilborn (1979)
93.7	30		10	10	Chiu and Hilborn (1979)
76.1	15	6	30		Agemian and Chau (1976b)

[A] Adapted from Tinsley et al. (1983)

[b] μg of chromium extracted/g of dust sample

[c] Acids are concentrated

[d] Molarity of solution

recent years. In this method, Cr(III) is co-precipitated with Fe(III) as hydroxide at a pH of 8-8.5 (Cranston and Murray, 1978; Pik et al., 1981). The co-precipitation of Cr(VI) has been accomplished by reducing Cr(VI) to Cr(III) by the addition of Fe(II) and subsequent co-precipitation of hydroxides of Cr(III) with Fe(II) at pH 8 (Cranston and Murray, 1978), or by co-precipitating Cr(VI) by Co(II) and ammonium pyrrolidinedithiocarbamate (APDC) addition (Pik et al., 1981). The co-precipitated chromium is filtered from the solution and analyzed by x-ray fluorescence or by flameless atomic absorption spectrometry.

4.2.3. Solvent Extraction. In this procedure, Cr(VI) is complexed with APDC at a pH of 1.8-3.0 and extracted with an organic solvent, typically methyl isobutyl ketone (MIBK). If Cr(III) is to be extracted, it must first be oxidized to Cr(VI) with reagents such as silver nitrate and potassium peroxydisulfate or with potassium permanganate and sodium azide (Towill et al., 1978). In the gas chromatographic procedure, chromium is chelated with 1,1,1-trifluoro-2,4-pentanedione or trifluoracetylacetone (HFTA) and the chelate is extracted into benzene. This method has been used by a number of investigators (Lovett and Lee, 1976; Gosink, 1976).

4.2.4. Chromatographic Method. A number of chromatographic materials including alumina, cation-exchange resin, anion-exchange resin, and chelating ion-exchange resin have been used for the cleanup of impurities from chromium samples. In the anion-exchange procedure, the solution containing Cr(VI) is allowed to pass through the resin bed at an optimum pH. The Cr(VI) retained on the resin bed is subsequently extracted with a suitable eluent. The major drawback of this procedure is that the recovery of Cr(VI) is often poor. The problem, however, has been alleviated by using an ascending flow technique or by in situ reduction of Cr(VI) by Fe(II) (Pankow and Janauer, 1974). Marino and Ingle (1981) used medium strength anion-exchange resin to obtain a satisfactory recovery of Cr(VI) from the resin bed.

In the cation exchange procedure, the resin is used to retain the cationic impurities while anionic Cr(VI) passed through the resin bed. This procedure has been used by Kneebone and Freiser (1975) for the analysis of Cr in occupational samples.

The chelatory ion-exchange procedure was employed by Leyden et al. (1972) to absorb quantitatively Cr(III) from a buffered solution. By this procedure, Cr(VI) was detected by reducing it to Cr(III) with the addition of sodium bisulfite.

The alumina procedure has been used for the separation of both Cr(III) and Cr(VI). Larochelle and Johnson (1978) adsorbed Cr(VI) on alumina column and used HCl for the subsequent elution of Cr(VI). Wolf et al. (1972), on the other hand, used an alumina column for the separation of Cr(III). In this procedure, Cr(III) is precipitated with other cations by the addition of excess 8-hydroxyquinoline. The dried precipitate is dissolved in chloroform, diluted with an equal volume of benzene, and passed through an activated alumina column. Chromium was eluted with a mixture of chloroform and benzene.

4.3. METHODS OF ANALYSIS

Chromium can be determined by a variety of analytical methods. A few analytical methods used for the determination of Cr are given in Table 4-2. It should be emphasized that the detection limit and the percent-relative standard deviation (% coefficient of variation) values given in Table 4-2 should be taken as values representative of the specific pretreatment techniques and

TABLE 4-2

Analytical Methods for the Determination of Chromium

Method	Type of Sample	Preconcentration	Selectivity	Detection Limit	% CV (at sample concentration)	Interference
Graphite furnace AA	blood, urine, and other biologic samples[a]	none	total Cr	0.1 μg/ℓ	5.2% (10 μg/ℓ)	Matrix interference can be avoided by wet ashing.
	natural waters[b]	co-precipitation with $Fe(OH)_3$	Cr(III); Cr(VI) can be reduced to Cr(III) by Fe(II)	0.001 μg/ℓ	5% (0.14 μg/ℓ)	none reported
	raw, treated, and distributed water[c]	none	total Cr	2 μg/ℓ	15% (2 μg/ℓ)	none reported
		APDC-MIBK extraction	Cr(VI); Cr(III) can be oxidized to Cr(VI)	0.6 μg/ℓ	20% (2 μg/ℓ)	none reported
Flame AA	raw, treated, and distributed water[c]	APDC-MIBK extraction	Cr(VI); Cr(III) can be oxidized to Cr(VI)	0.05 μg/ℓ	5% (3 μg/ℓ)	none reported
	natural water[d]	anion exchange	Cr(VI)	0.1 μg/ℓ	20% (0.1 μg/ℓ)	none reported
	blood, urine, and other biologic samples[e]	MIBK extraction	Cr(VI)	10 μg/ℓ	15% (25 μg/ℓ)	none reported
Spectrophotometric	tissue samples[f]	APDC-MIBK extraction	Cr(VI); Cr(III) can be oxidized to Cr(VI)	1.2 μg/ℓ	0.4% (800 μg/ℓ)	Fe, Ni and PO_4^{3-} may interfere
Catalytic method	air particulates[g]	none	Cr(VI)	1 ng	6% (<100 μg/ℓ)	Pb, Cu, Cr(III), Fe(III), and V(V) may interfere
Neutron activation	air particulates[h]	none	total Cr	30 ng/n[i]	15% (1.3 ng/m^3)	none reported
	freshwater[j]	none	total Cr	0.12 μg/ℓ	21% (1.4 μg/ℓ)	none reported

TABLE 4-2 (cont.)

Analytical Methods for the Determination of Chromium

Method	Type of Sample	Preconcentration	Selectivity	Detection Limit	% CV (at sample concentration)	Interference
Gas chromatography (electron capture detection)	natural waters^k	HTFA-benzene extraction	Cr(III) and Cr(VI)	0.1 μg/ℓ	2.6% (1.9 μg/ℓ)	none reported
Gas chromatography (AAS detection)	blood, serum, orchard leaves^l	HTFA-benzene extraction	Cr(III)	<1 ng	<6% (1 ng)	none reported
Gas chromatography (MS detection)	blood^m	HTFA-benzene extraction	Cr(III)	0.5 pg	9% (10 ng/g)	none reported
Liquid chromatography (coulometric detection)	natural water^n	1 ℓ sample concentrated to 10 mℓ	Cr(VI)	0.8 μg/ℓ	<2% (90 μg/ℓ)	SO_4^{-2}, PO_4^{3-} may inerfere
X-ray fluorescence (energy dispersive)	dried solution deposit^o	none	total Cr	1.5 μg/g^p	9% (1 μg/cm^2)	absorption by matrix and difference in particle size may cause error
X-ray fluorescence (energy dispersive)	surface water and drinking water^q	chelating ion-exchange membrane	Cr(III)	0.8 μg/ℓ	10-15% (1 μg/ℓ)	excess alkali and alkaline earth metals may interfere
Differential pulse polarography	natural waters^r	none	Cr(VI)	10 μg/ℓ	34% (61 μg/ℓ)	excess Cu(II) and Fe(III) may interfere
Emission spectroscopy (inductively coupled plasma source)	natural waters^s	none	total Cr	1.8-6	≈5%^{t}	none reported
Mass spectrometry	variety of samples^u	none	total Cr	0.05-1 μg^v	20% (photographic) 3% (electrical) 0.5% (isotope dilution)	Any species having the same m/e ratio as Cr nuclide may interfere

TABLE 4-2 (cont.)

Analytical Methods for the Determination of Chromium

Method	Type of Sample	Preconcentration	Selectivity	Detection Limit	% CV (at sample concentration)	Interference
Chemiluminescence	natural waters and orchard leaves[w]	none	Cr(III)	0.02 µg/ℓ	20% (at 2.3 ppm)	Fe(III), Fe(II), Co(II), SO_3^{2-}, and NO_2^- may interfere
Chemiluminescence (lophine)	natural waters[x]	ion exchange resin	Cr(VI)	0.015 µg/ℓ		Fe(III), Fe(II), Co(II), Cr(III), Mno_4^-, and other cations and anions may interfere
PIXE (Particle Induced X-ray Emission)	ambient air[y]; biological samples[z]	none	total Cr	<1 ng	<35%	inadequate sample preparation; Fe may interfere

[a] Davidson and Secrest, 1972

[b] Cranston and Murray, 1978

[c] Méranger et al., 1981

[d] Pankow and Janauer, 1974

[e] Feldman et al., 1967

[f] Bryson and Goodall, 1981

[g] Kneebone and Freiser, 1975

[h] Demuynck et al., 1976

[i] Bhagat et al., 1971

[j] Salbu et al., 1975

[k] Lovett and Lee, 1976

[l] Wolf, 1976

[m] Wolf et al., 1972

[n] Larochelle and Johnson, 1978

[o] Camp et al., 1975

[p] Kuhn, 1973

[q] VanGrieken et al., 1977

[r] Crosmun and Mueller, 1975

[s] Quinby-Hunt, 1978

[t] Boumanns and deBoer, 1972

[u] Ahearn, 1972

[v] Elser, 1976

[w] Hoyt and Ingle, 1976

[x] Marino and Ingle, 1981

[y] Metternich et al., 1981

[z] Bartsch et al., 1982

instrumental methods used rather than definite data. For example, both the detection limit and percent CV values obtained by the same instrumental method may vary several-fold depending on the extent of preconcentration of the sample and the method used for eliminating interferences. These values may also vary considerably from laboratory to laboratory and even within the same laboratory. Part of the errors in measurement occur from the absence of low level standard reference materials. Several methods for analyzing chromium are described briefly below.

4.3.1. Atomic Absorption Spectrometry (flame). This method has been used by various investigators for the determination of Cr in surface water, sewage effluent, and biological samples. The determination of Cr by the air-acetylene flame is prone to interference by other elements (Thompson and Wagstaff, 1979). This problem can be avoided by using nitrous oxide-acetylene flame but this results in a decrease in the detection limit (Thompson and Wagstaff, 1979). Therefore, most investigators have used air-acetylene flame for the determination of Cr. However, for samples with low Cr concentration, pretreatment of the samples providing preconcentration of Cr and the reduction of the interfering effects from other ions are required. Thompson and Wagstaff (1979) used an evaporative technique on a hot plate to concentrate the sample 5-fold. A 2% ammonium perchlorate solution (W/V) was used to suppress the interelement interference effects. Better methods for pretreatment of samples include ion-exchange separation (Pankow et al., 1977; Pankow and Janauer, 1974), APDC-MIBK extraction (Gilbert and Clay, 1973) and MIBK extraction (Feldman et al., 1967). The flame AAS technique is not a preferable method for samples with very low Cr concentration since this method has a much higher detection limit than flameless AAS (Slavin, 1981).

4.3.2. Atomic Absorption Spectrometry (flameless). In the flameless AAS method, the sample is atomized directly in a graphite furnace, carbon rod, or tantalum filament instead of a flame. It is one of the most attractive methods for the analysis of solid and liquid biological samples since the method does not generally require sample preparation. Despite the high sensitivity of the flame less AAS method, it may suffer from certain disadvantages. For example, matrix interference, background or nonspecific absorption effects, volatilization of some Cr during dry ashing, and adsorption of Cr on the walls of crucibles during dry ashing can cause error in analysis. The matrix interference effect in the case of water samples can be overcome by chelation and solvent extraction (Meranger et al., 1979, 1981) or by the co-precipitation technique (Cranston and Murray, 1978), and in the case of biological samples, by wet disgestion (Davidson and Secrest, 1972) prior to introduction of the sample into the graphite furnace. The Zeeman background correction systems for non-specific absorbance are those most recommended for the analysis of Cr (see handbooks on EAAS by Perkin-Elmer and Hitachi). Other background correction systems include the dueterium arc corrector (Cranston and Murray, 1978), and, by continuum source, echelle, wavelength-modulated, atomic absorption spectrophotometer (CEWM-AA) (Kumpulanen et al., 1979; Veillon et al., 1982a,b). The volatilization of Cr during dry ashing at temperatures of 700°C or higher, particularly during the analysis of complex matrices such as food, may be substantial (Kumpulainen et al., 1979). Low temperature ashing, for example, with oxygen plasma at 150°C, would eliminate this problem and the problem of Cr adsorption on crucible walls. However, the low temperature ashing may not be suitable for some biological samples (bovine liver), and some biological materials such as brewer's yeast may contain acid insoluble material that can strongly adsorb chromium (Kumpulainen et al., 1979). However, these problems have been overcome by utilizing dry ashing at 500°C with sulfuric acid and hydrogen peroxide as ashing acids (Kumpulainen et al., 1979). The problems of sorption and volatilization can also be eliminated by the use of "platform" technique described by Slavin (1981).

Versieck et al. (1978) reported that chromium levels in serum from normal subjects was 0.16 μg/ℓ when determined by carefully conducted neutron activation analysis. In a survey of previous reports of chromium levels determined by flameless AAS, the range of values was 0.73 to 150 μg/ℓ, and the levels tended to become lower as improvements in detection limits occurred. These results prompted an intensive study of possible sources of artifacts in the flameless AAS analysis of biological fluids by Kayne et al. (1978) and Guthrie et al. (1978). Guthrie et al. (1978), in a study of the effects of purge gas, char temperature, sample volume, and graphite tubes on the determination of low ppb levels of chromium, demonstrated that all these parameters affected the background non-atomic absorption, and that there was a direct correlation between background absorption and the apparent chromium content of the sample. It was suggested that the background correction was inadequate as the result of the low intensity of the D_2 lamp at the near UV wavelength used in chromium analysis. Kayne et al. (1978) came to a similar conclusion, and modified the background correction by replacing the usual D_2 lamp with a tungsten halogen lamp. This modification provided adequate background correction, and serum chromium levels determined for 8 normal male subjects averaged 0.14 μg/ℓ, while most measurements from 66 randomly chosen urine samples were ≈0.9 μg/ℓ. Guthrie et al. (1978), Kayne et al. (1979), and Anderson (1981) noted that earlier reports of chromium levels in urine and serum should be considered artificially high (by about an order of magnitude) in light of these findings.

4.3.3. Emission Spectroscopy. In emission spectroscopy, prepared samples are excited with a flame, arc, spark, or plasma and the resulting light is dispersed with a monochromator. The characteristic emission lines of the excited elements are recorded electronically or on a photographic plate. Because of its better sensitivity, inductively compiled plasma atomic emission spectrometry (ICP-AES) has been more extensively used in recent years than the other modes of excitation (Towill et al., 1978; Slavin, 1981). Since the sample is generally introduced into the plasma source by pneumatic nebulization, all solid and biological samples require wet digestion prior to analysis. The wet digestion also tends to minimize the matrix effects. A HF/HNO_3 digestion at 170°C has been employed for the simultaneous multi-element analysis of air particulate matters (Broekaert et al., 1982). Similarly, wet digestion by direct chelation with 1,1,1-trifluoro-2,4-pentaedione (also known as trifluoroacelytacetone) (HTFA) or hexafluoroacetylacetone (HHFA) has been used for the cleanup and volatilization of Cr in biological samples (Black and Browner, 1981) prior to ICP-AES analysis. Recently, a direct atomization technique for raw agricultural crop samples has been presented (Kuennen et al., 1982). The technique employs a 30-minute pressure dissolution of sample composite with 6M HCl at 80°C in linear polyethylene bottles. The dissolved samples after proper filtration by Teflon filters can be aspirated directly into the plasma source. Combined with real sample matrix calibration technique, it has been suggested that this method provide comparable recovery and precision as obtained by the more time-consuming conventional wet ashing methods.

4.3.4. Neutron Activation Analysis. Neutron activation analysis is one of the most sensitive modern analytical techniques for the determination of trace elements. Neutron activation analyses are applicable to many kinds of environmental samples including air particulates, dusts, soils, fresh and marine water, sediments, biological liquids and solids, and foods. The samples are often irradiated without prior chemical treatment. A detection limit of 0.12 μg/ℓ in freshwater (Salbu et al., 1975) and 0.2 μg/g in biologic materials (Spyrou et al., 1974) has been reported for samples analyzed without chemical processing. Lower detection limits generally can be achieved if the samples are chemically processed to separate and concentrate chromium. For example, in the chemical processing of samples typically by ion-exchange separation, detection limits of 0.1 ng/ℓ for river water, 3 ng/ℓ for seawater, in the ppb range for biological samples and the ng/m^3 range for ambient air have been reported (McClendon, 1974; Robertson and Carpenter, 1974; Kowalczyk et al., 1982; Lin, 1983).

One distinct advantage of this method is the reduced problems arising from reagent contamination. Even if chemical processing is required, post-irradiation contamination is of no consequence in introducing error to the final result. In addition to the problem of acquiring a neutron source, this method has another disadvantage. Due to the intense x-ray or bremsstrahlung activity from ^{24}Na, ^{38}Cl, ^{42}K, ^{56}Mn, and ^{32}p in many samples, the irradiated samples usually must be cooled for several weeks before measuring Cr concentration. However, chemically separating the offending nucleides can reduce the cooling period to about 24 hours (McClendon, 1974).

4.3.5. X-ray Fluorescence. The x-ray fluorescence method is commonly applied to solid samples. In this technique, the sample is bombarded with high energy photons, for example, low energy x-ray or gamma photons or with particles such as protons. The intensity of the characteristic emitted x-ray is currently measured by two techniques, namely, energy-dispersive analysis and wavelength-dispersive analysis. The resolution of wavelength-dispersive analysis is much better than energy-dispersive analysis which often permits the former method to determine the oxidation states of an element (Quinby-Hunt, 1978).

This technique is useful for trace analysis in solid samples, namely, air particulates (collected on filters), sediments, biological specimens, and filtered suspended solids from aqueous media. However, for aqueous samples, sample preparation leading to the deposition of the element on a filtering medium is required. This deposition can be done by a variety of methods. The obvious and simple method is the evaporative drying of the sample on a Mylar film (Tanaka et al., 1981). Other methods of sample deposition include retention on chelating filters (Smits and Van Grieken, 1981), vapor filtration technique (Greathouse and Craun, 1978) and co-precipitation (Pik et al., 1981). The last three methods not only allow deposition of Cr on a filtering media, but also permit separation and concentration of Cr from the aqueous phase during the deposition step.

Sample preparation in the case of solid samples is an important requirement for this method. In order to avoid absorption and scattering by sample matrix, the size and shape of the particles on the films should be controlled by pressing the deposits into thin wafers (Towill et al., 1978).

4.3.6. Colorimetric. The diphenylcarbazide colorimetric method is the most commonly used for monitoring chromium compounds. Either through the oxidation of Cr(III) or direct reaction with Cr(VI), this method was proposed by NIOSH (1976) as a "Draft--subject to review" procedure for measuring Cr(VI) in occupational atmospheres. While it is sensitive to 10 and 50 μg samples, it has poor sensitivity for samples of 0.5 and 1 μg. (Bhargava et al., 1983). The method may not be suitable for use with welding fumes. Instead, a carbonate leaching method has been described for the determination of Cr in welding fumes and other complex matrices (Thomsen and Stern, 1979). Bryson and Goodall (1981) have described a modified diphenylcarbazide spectrophotometric method for the determination of Cr in biological tissues.

4.3.7. Gas Chromatography.

The gas chromatographic method is suitable for a variety of environmental samples. The analysis of water samples by this method does not generally require pretreatment before complexation (Lovett and Lee, 1976). Samples that are solid, namely, particulate matter, and biological samples are first digested to get Cr in solution. The Cr is then quantitatively chelated with 1,1,1-trifluoro-2,4-pentanedione (HFTA) or hexafluoroacetylacetone (HHFA) to form a thermally stable, volatile Cr(III) complex. To determine Cr(VI), it should be reduced to Cr(III) by a reducing agent, such as sodium sulfite. The Cr(III)-HFTA or Cr(III)-HHFA complex is extracted into an organic solvent, usually benzene or hexane, and an aliquot is injected into the GC column. Recently a direct chelation (without pretreatment) method has been described for biological samples (Black and Browner, 1981).

The detection of Cr(III) complex can be accomplished by a variety of detectors. The sensitivity of this method is dependent on the detector used. A number of detectors including electron capture (Lovett and Lee, 1976), atomic absorption (Wolf, 1976), mass spectrometric (Wolf et al., 1972), and ICP-AES (Black and Browner, 1981) have been used.

The gas chromatography with any of the detection methods described has excellent sensitivity for Cr determination, but the mass spectrometric method is extraordinarily sensitive and specific.

4.3.8. Chemiluminescence. Luminal (5-amino-2,3-dihydrophthalazine-1,4-dione) and lophine (2,4,5-triphenylimidazole) emit light when oxidized by hydrogen peroxide. The first oxidation in basic solution is catalyzed by Cr(III) and the second by Cr(VI). The design of different chemiluminescence instruments for the determination of Cr vary primarily in the technique for mixing the sample and reagents. The three types of sample modules which are commonly used are discrete sampling system, flow system, and centrifugal analyzer (Hoyt and Ingle, 1976). All these sample modules have been used for the analysis of Cr (Towill et al., 1978).

The chemiluminescence method has been used primarily for the analysis of Cr in water and in biological samples (Marino and Ingle, 1981; Hoyt and Ingle, 1976). The method is fast, economical, and has a high sensitivity. The sensitivity can be further increased by preconcentration of the samples (Marino and Ingle, 1981). However, this method has not been as widely used as some of the other methods.

4.3.9. Polarography. Two recent variations of the method, namely, single-sweep polarography and differential pulse polarography, have both been used for the detection of Cr in natural waters (Whitnack, 1975; Crosmun and Mueller, 1975). The polarographic method has a comparatively lower sensitivity than other methods and is not currently popular for Cr analysis.

4.3.10. Mass Spectrometry. The spark-source mass spectrometric method is applicable to virtually any matrix, but the results are only semiquantitative (Towill et al., 1978). The precision and accuracy of this method can be greatly improved by using the isotope dilution technique. This method has been used to establish the Cr content in NBS bovine liver (Dunstan and Garner, 1977). The mass spectrometric method is rarely used for the routine determination of chromium.

4.3.11. Catalytic Method. This method has been used for the determination of Cr(VI) in occupational samples (Kneebone and Freiser, 1975). In this method, the microdetermination of Cr(VI) is done by means of Cr catalyzed oxidation of o-dianisidine by hydrogen peroxide. The reaction rate is monitored spectrophotometrically. This method has limited application (occupational samples) because of interferences by various cations, and it is rarely used for the determination of Cr.

4.3.12. Liquid Chromatography. This method in combination with a coulometric detection has been used for the determination of Cr in water samples (Larochelle and Johnson, 1978). In this method Cr(VI) is separated by an alumina column and the separated solution is passed through a flow-through coulometric detector. Although the method has been purported to have good sensitivity and precision, it has found little application in the analysis of chromium.

4.3.13. Particle Induced X-ray Emission. Particle Induced X-ray Emission (PIXE) has been used to analyze elemental constituents of particulate matter. PIXE was first introduced by Johansson and Johansson (1970) and has found wide use in elemental analysis of atmospheric aerosols and considerably less use for biological samples. In this method, atoms of interest are bombarded by protons. The incident particles will interact with the atoms to eject electrons, thereby ionizing the atoms. The characteristic X-rays emitted are proportional to the atomic number (Z^2). PIXE analysis of elemental Cr is sensitive to the nanogram level; it is a rapid, multielemental, nondestructive technique which requires no chemical breakdown of the sample. However, elaborate sample preparation and highly skilled operators are required for successful analyses (Metternich et al., 1982; Bartsch et al., 1982).

4.4. CONSIDERATIONS IN ANALYSIS

The determination of Cr in samples containing trace amounts of the compound requires special precautionary measures from the initial sample collection step to the final analytical manipulations of the samples (Zief and Mitchell, 1976). For example, contamination of samples during collection should be avoided by the use of Cr-free equipment. This is particularly true for the collection of biological samples with stainless steel needles, scalpels, trays and utensils which may contain 18% chromium. Similarly, sample containers should be free from the possibility of sample contamination. Polyethylene bottles and bags are particularly suitable as sample containers. Even with polyethylene bottles, adsorption of Cr on the surface of the container from water samples may be a serious problem. Therefore, acidification of aqueous samples prior to storage is necessary to avoid adsorption losses.

The possibility of sample contamination and losses during analytical pretreatment of the samples should be avoided. Care should be taken that only reagents of the highest purity are used. Even so, the quantity added should be limited to a minimum to avoid unnecessary buildup of contaminants. The use of Cr-containing grinding or homogenizing equipment can introduce Cr-contamination into the samples. Grinding such samples with an agate mortar and pestle is a better procedure. The analysis of Cr, especially in biological samples, is complicated by extreme matrix effects, possible volatility of some Cr complexes, and the inherent property of Cr-complexes to bind non-specifically to reaction vessels, graphite tubes, or other equipment. The methods used to minimize these problems have been discussed in section 4.3.2.

The problem of developing accurate data from Cr analysis, particularly in food and biological samples, is amply illustrated by the large variations in the interlaboratory comparison data (Towill et al., 1978). The problem is further aggravated by the non-availability of Standard Reference Materials (SRM). Only recently has the National Bureau of Standards (NBS) issued materials certified for Cr, such as brewer's yeast (SRM-1569), bovine liver (SRM-1577), orchard leaves (SRM-1571), spinach leaves (SRM-1570), pine needles (SRM-1575), and tomato leaves (SRM-1573). In view of the absence of suitable comparison with SRMs, the older data should be interpreted with skepticism.

Another problem in dealing with the analytical methods is their ability to distinguish between Cr(III) and Cr(VI). This is particularly important since Cr(VI) has been associated with health hazards, while Cr(III) is of substantially less concern and is in fact necessary (at very low but as yet undetermined levels) for the maintenance of a normal glucose tolerance factor (Marino and Ingle, 1981). The problem for the determination of the two oxidation states of Cr is not critical in foods, sediments, soils, and biological samples, because Cr is genrally present in the Cr(III) state in these samples. However, Cr may be present in both oxidation states in ambient and occupational air, and in water samples. It should also be recognized that Cr(VI) may be present in both water soluble and water insoluble form in these samples. It is necessary to distinguish these two forms of Cr(VI), as they may have different genotoxic properties (Thomsen and Stern, 1979). Some of the methods that distinguish between Cr(VI) and Cr(III) have already been discussed. The analytical method for the determination of soluble and insoluble forms of Cr(VI) in occupational air samples has been described by Thomsen and Stern (1979).

5. CHROMIUM METABOLISM IN MAN AND ANIMALS

5.1. ROUTES OF CHROMIUM ABSORPTION

5.1.1. Chromium Absorption and Deposition by Inhalation. An important route of exposure to chromium compounds is through inhalation of chromium containing aerosols. In general, during inhalation (and exhalation) a portion of the inhaled aerosol may be deposited by contact with airway surfaces or be transferred to unexhaled air. The remainder is exhaled. The portion transferred to unexhaled air may be either deposited by contact with airway surfaces or later exhaled. These phenomena are complicated by interactions that may occur between the particles, other gases and the water vapor present in the airways (U.S. EPA, 1982). As such, the deposition and retention patterns for chromium aerosols depend on the size and solubility of the particular chromium compound.

Chromium aerosols occur mainly in the small particle-size fractions. The oxidation state of the Cr compound depends on the emission process as well as the atmospheric interactions. In metallurgy, most of the chromium released is elemental or trivalent (NAS, 1974). In the chemical industry, chromate dust from the processing of chromite ore averaged 0.32 to 0.37 μm in diameter (Gafafer, 1953). Fly ash from coal-fired electric power plants contained Cr in the 1-2 μm size fractions (Davidson et al., 1974). Combustion processes under alkaline conditions are conducive to the formation of Cr(VI). The distribution of chromium in the human lung was investigated by Bartsch et al. (1982), who examined 35 lung pairs obtained during autopsy from randomly selected patients in Liege, Belgium, an area containing many steel plants and foundries. Using PIXE analysis (Particle Induced X-ray Emission), they found that Cr concentrations in the lung averaged 2.85 μg/g (ppm) dry matter, with the largest amounts occurring in the lymph nodes. The remaining chromium was distributed over a gradient toward the apexes of the lungs, suggesting to the authors a relation to the normal distribution of inspired air and contaminants during normal breathing.

Langard et al. (1978) exposed rats to zinc chromate(VI) dust at a concentration of 7.35 mg/m^3. Before exposure, the mean blood chromium concentration was 0.007 μg/mℓ (ppm). Following exposure, values were 0.024, 0.22, and 0.31 μg/mℓ (ppm) at 100, 250, and 350 minutes, respectively.

The next portion of the study involved four consecutive daily exposures of 6 hours duration to zinc chromate at a level of 7.35 mg/m^3. Blood concentrations appeared to peak after the second exposure session. Mean blood chromium values from samples taken immediately after each exposure session were: 0.30, 0.56, 0.46, and 0.34 μg/mℓ (ppm) for days 1 through 4. The mean blood chromium level following 2 months of exposure for 6.5 hours/day, 5 days/week was quite similar, 0.495 μg/mℓ (ppm). There were no significant differences in absorption, as reflected by blood chromium level, between the sexes or between day and night exposure regimens. Kamiya et al. (1981) exposed rats to chromite dust for 28 days to determine distribution and retention of total Cr from inhalation exposure. While data are limited, qualitative conclusions can be drawn. Whole blood total Cr levels measured at various times throughout the exposures remained about the same from days 5 through 28. The highest Cr concentrations were found in the kidney followed in decreasing order by the lung, spleen, liver and blood. Concentrations in the liver were similar to those in the blood, changing little from days 5 to 28. Levels in the lung, kidney and spleen were cumulative.

Baetjer et al. (1959a) exposed guinea pigs via intratracheal administration to 200 μg chromium as sodium chromate(VI), potassium dichromate(VI), or chromic

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chloride(III), all of which are water soluble salts. For the Cr(VI) compounds 10 minutes post-instillation, 15% of the dose remained in the lungs, 20% was found in the blood, and 5% was distributed among various soft tissues. Clearance of chromium upward from the trachea and subsequent swallowing is assumed to account for the majority of the dose not found in the blood and tissues. During the first 24 hours, ≈13% of the dose was excreted, 11% remained in the lungs, and 16% was found in the blood and other tissues. After 140 days, chromium had been essentially cleared from all tissues except lung and spleen. For chromic chloride(III) 10 minutes post-instillation, 69% of the administered dose was retained in the lungs, with 4% in the blood and other tissues combined. Twenty-four hours post-exposure, the lungs retained 45% of the administered dose; lung retention after 30 and 60 days was 30 and 12%, respectively.

Of the water soluble salts studied, Cr(III) is absorbed much more slowly from the lungs than Cr(VI), possibly as a result of binding to extracellular macromolecules. In addition, analyses of lungs from experimental animals and human autopsy specimens indicate that water soluble salts undergo conversion to very insoluble moieties with long residence times in lung tissue (Baetjer et al., 1959a).

Wada et al. (1983) exposed male SD strain rats to $CrCl_3$ at an atmospheric concentration of 14.1 mg/m^3 (Cr), and observed that the chromium was associated with both high and low molecular weight proteins. The chromium which remained in the lungs was associated with the high molecular weight fraction and this fraction slowly decreased with time following exposure. The level of chromium associated with the low molecular weight fraction remained constant for the 5 observation days following treatment; however, chromium associated with this fraction accumulated with time in the liver. The authors suggested that the low molecular weight protein was involved in the absorption and transport of chromium following inhalation. Low molecular proteinuria was also noted in rabbits receiving subcutaneous injection of 1.77 mg Cr(VI)/kg body weight (Nomiyama et al., 1982).

Visek et al. (1953) also studied the fate of $^{51}CrCl_3$ following intratracheal instillation. Seven days post-exposure, 55% of the chromium was excreted in the feces and 7% in the urine. These data agree with Baetjer et al. (1959a), in that a large portion of the administered dose appears to have been cleared to the gastrointestinal tract. Tissue concentrations in this study indicated that ≈5% of the administered dose was absorbed from the lungs.

No data are available which could be used to accurately estimate total pulmonary absorption following inhalation exposure. The contribution of gastrointestinal absorption to body burden following inhalation or intratracheal exposure is not clear.

5.1.2. Gastrointestinal Absorption of Chromium. Gastrointestinal absorption of chromium also appears to be dependent on valence state. Donaldson and Barreras (1966) examined absorption of $^{51}CrCl_3$(III) and $Na_2{}^{51}CrO_4$(VI) in rats and in humans and conducted a series of in vitro evaluations to clarify factors affecting absorption.

Based on fecal excretion, mean absorption of orally administered ^{51}Cr compounds in human patients was ≈0.4% for $CrCl_3$ and ≈10.6% for Na_2CrO_4. Approximately 0.5 and 2.1% of the doses of $CrCl_3$, respectively, were excreted in the urine after 24 hours. When $CrCl_3$ was administered intraduodenally, absorption of $CrCl_3$ was not appreciably increased; however, intraduodenal administration of $NaCrO_4$ resulted in an estimated 50% absorption.

In rats, ≈2% of the intragastric dose of both $CrCl_3$ and Na_2CrO_4 appeared to be absorbed based on fecal excretion (i.e., it was assumed that any radioactivity not recovered in the feces represented the absorbed portion of the dose, although it should be noted that the percision of these estimates may be questioned). Jejunal administration increased apparent $CrCl_3$ absorption to 8%, while Na_2CrO_4 was increased to ≈25%. Similar low levels of absorption of less than 1% were estimated by determining whole body counts 2 days after administration of radiolabeled $CrCl_3$ or Na_2CrO_4 (Sayoto et al., 1980).

In vitro studies by Donaldson and Barreras (1966) showed that $CrCl_3$ (III) was bound by both neutralized and acid gastric juice, while Na_2CrO_4 (VI) was bound by acid gastric juice alone. Binding effectively prevented uptake by intestinal sections. Acid gastric juice, in addition to binding Na_2CrO_4 (VI), also was capable of reducing Cr(VI) compound to Cr(III).

These absorption values must be considered rough estimates. Short-term urinary excretion values cannot take into account either deposition of chromium into body sinks or the potential contribution of intestinal excretion. Absorption estimates by difference from fecal excretion also cannot take into account the potential role of enterohepatic cycling.

MacKenzie et al. (1958) administered either K_2CrO_4 (VI) or $CrCl_3$ (III) in the drinking water to rats at 25 mg/ℓ (ppm). After 1 year of exposure, animals receiving the hexavalent compound had average tissue levels that were 9 times higher than those receiving the trivalent salt. This was interpreted to indicate much greater gastrointestinal absorption of the hexavalent salt. The possible role of differences in elimination kinetics was not addressed.

Mertz et al. (1965) administered a single dose of 0.15, 1.0, or 10 μg $^{51}CrCl_3$/g body weight by stomach tube to rats. By comparing whole body radioactivity 4 to 10 days after an intragastric dose with that following an intravenous dose, they suggest 2 to 3% as a rough estimate of gastrointestinal absorption. Absorption was found to be independent of dose level or dietary chromium history (deficient versus supplemented). (Doisy (1971) estimated absorption at 0.5%.

Visek et al. (1953) gave a single dose of $CrCl_3$ (III) by gavage to rats. Tissue distribution indicated <0.5% absorption after 4 days. Urinary excretion suggested higher absorption estimates, but fecal contamination of the samples was suspected.

MacKenzie et al. (1959) administered Na_2CrO_4 (VI) as a single dose by stomach tube. Urinary excretion of 6% of the dose after 14 days in fasted rats and 3% in non-fasted rats was observed and used as an estimate of absorption. Blood chromium concentrations when rats were given Na_2CrO_4 were 2-fold higher than for animals given $^{51}CrCl_3$. This is not surprising, since Cr(III) is cleared from the serum much more rapidly than Cr(VI) disappears from the erythrocytes. Urinary excretion data for Cr(III) compound were not reported.

Additional evidence for the poor absorption of $CrCl_3$ (III) was presented by Mertz et al. (1965). They found that a 100-fold greater oral dose was required to alter glucose tolerance in rats than the intravenous effective dose.

Ogawa (1976) examined differences in absorption and metabolism via several routes of exposure using CrCl (III) and Na_2CrO (VI) administered to rats. They found gastrointestinal absorption to be 2.4 and 1.4%, respectively, for the two salts. When animals were fasted for 48 hours, absorption of both salts was increased to 11%.

Although precise quantitation of absorption efficiency is impossible, a reasonable estimate from the available literature discussed above is that both valence states are absorbed at efficiences of <5%.

5.1.3. Chromium Absorption Through the Skin. Percutaneous absorption of chromium appears to be related to valence state, the particular salt employed, and the concentration applied.

Mali (1963) conducted a series of _in vitro_ and _in vivo_ studies to determine penetration of potassium dichromate(VI) and chromic sulfate(III) through the skin (the source of skin was not mentioned). They found that neither compound diffused spontaneously through intact, isolated epidermal membranes. The diffusion constant for diffusion of the Cr(VI) compounds through dermis (314×10^{-6} cm^2/min) indicated unimpeded absorption; however, the diffusion constant for the trivalent compound was 26.6×10^{-6} cm^2/min.

Significant amounts (30%) of Cr(III) were bound to dermal proteins _in vitro_, while only very small amounts (1%) of Cr(VI) were bound (Mali, 1963). These results were confirmed in human volunteers. It was found that _in vivo_ potassium dichromate but not chromic sulfate penetrated intact epidermis. In addition, reduction of Cr(VI) to Cr(III) in the skin tissue was demonstrated. The rate of this reduction was pH dependent.

Samitz and Katz (1963, 1964) presented additional data which indicate that Cr(III) binds to skin _in vitro_, and that binding following exposure to Cr(VI) salts is dependent upon reduction to Cr(III).

Samitz and Gross (1961) presented preliminary evidence that there is no difference in absorption of potassium dichromate(VI) as compared to chromium nitrate(III) _in vivo_ in guinea pigs. Samitz and Shrager (1966) reported additional evidence that permeability of the skin to Cr(III) is dependent upon which salt is employed. Their data indicate that absorption of chromic sulfate is negligible, absorption of chromium nitrate is somewhat greater than chromic sulfate absorption, and absorption of chromic chloride is as great as potassium dichromate. Waklberg (1968) noted that percutaneous absorption of sodium chromate was greater at pH 6.5 and higher compared with pH 5.6 and lower.

Wahlberg (1965) reported that absorption of a given salt is dependent upon the concentration applied. In this study, application of 0.017 M to 0.239 M solutions of Cr(III) resulted in percentages of absorption which were not statistically different from absorption experiments under the same conditions for Cr(VI). However, at concentrations from 0.261 to 0.398 M, significantly more of the Cr(VI) compound was absorbed. Absolute absorption rates for chromic chloride were maximal with application of 0.239 to 0.261 M solutions, reaching levels of 315 to 330 n moles Cr/hour/cm^2. In contrast, absorption rates of sodium dichromate reached a maximum of 690 to 725n moles Cr/hour/cm^2 at a concentration of 0.261 to 0.398 M, the maximum absorption was 4% for the 0.261 M solution.

In conclusion, percutaneous absorption of chromium is dependent on valence state, anionic form, the concentration and pH of the applied solution.

5.2. CHROMIUM TRANSPORT, METABOLISM, DISTRIBUTION, AND ELIMINATION

5.2.1. Transport and Metabolism. The mechanism of chromium transport is dependent upon the valence state after reaching the bloodstream. Cr(VI) readily crosses erythrocyte membranes. Kitagawa et al. (1982) demonstrated *in vitro* the inhibition of Cr(VI) penetration into erythrocytes by 4-acetamido-4'-isothiocyano-stilbene-2,2'-disulfonic acid, an inhibitor of anion transport. After entry, the Cr(VI) undergoes reduction to Cr(III) and this reduction has been investigated in other cell systems. In studies with cultured hamster fibroblasts, Levis et al. (1978) have shown that only Cr(III) could be identified intracellularly following treatment with potassium dichromate. The mechanism for intracellular reduction is not completely understood. Several investigators have proposed a role for the mixed function oxidases. These proposals are based upon the reduction of mutagenic activity following addition of microsomal preparations to Cr(VI) (Gruber and Jennette, 1978; Lofroth, 1978; Petrilli and DeFlora, 1978a). While rat liver preparations are very effective in reducing mutagenic activity, lung preparations show only minimal activity (Petrilli and DeFlora, 1978b). Addition of reduced cofactors, such as GSH, NADH, or NADPH, also resulted in reduced activity. Langard (1979) presented evidence that although reduction of Cr(VI) may take place at any intracellular site where electron donors are available (which includes the microsomes), the primary site of reduction is within the mitochondria. In relation to chromium binding to hemoglobin, Kitagawa et al. (1982) reported that the reduced cofactor GSH was necessary for the *in vitro* binding of Cr(VI) to purified hemoglobin, suggesting that either the chromium or the hemoglobin has been reduced for binding to occur. Evidence that the reduction of Cr(VI) to Cr(III) may be of biological importance was provided by Aaseth et al. (1982). Cr(VI) was shown to bind to erythrocytes under *in vitro* incubation conditions. When GSH was added to the incubation media, the binding of chromium to the erythrocytes decreased as a result of the reduction of Cr(VI) to Cr(III) and the inability of Cr(III) to penetrate the cell membrane (Aaseth et al., 1982). Reduction of chromium binding was also observed when intracellular GSH was decreased by the action of diethylmaleate. In this case, it was proposed that the lower binding resulted from the failure to reduce Cr(VI) to Cr(III) in the cytosol. Jennette (1982) demonstrated that a Cr(V) intermediate was formed during the *in vitro* reduction of Cr(VI) to Cr(III) by rat liver microsomes and that this intermediate may be the chemically reactive form of chromium.

Localization *in vivo* of Cr(III) within the body cells of the rat appears to be time dependent, with initial high concentrations within the cytosol and subsequent translocation to mitochondrial and nuclear fractions (Langard, 1979). In addition, the partitioning of intracellular chromium appears to be dose related. Tandon et al. (1979) found that chromium nitrate(III) doses of 1, 2 or 3 mg/kg administered intraperitoneally resulted in an increased percentage in the mitochondrial fraction with increasing dose. Early hypotheses assumed intracellular binding of Cr(III) to proteins; however, in vitro data developed by Sanderson (1976) indicated that intracellular chromic ion exists in the form of coordination complexes with small organic anions. For Cr(VI), Alexander et al. (1982) found that the relative chromate uptake in rat liver mitochondria decreased with increasing chromate dose.

Transport of Cr(III) is facilitated by specific binding with transferrin (Hopkins and Schwartz, 1964). Following very large doses, binding with other serum proteins occurs. Red blood cells appear to be essentially impermeable to Cr(III). Impermeability of all cell membranes to Cr(III) compounds has been traditionally accepted; however, Levis et al. (1978) have shown uptake of $CrCl_3$ by cultured hamster fibroblasts. In addition, Tandon et al. (1979) have shown significant intracellular levels of chromium following in vivo exposure to Cr(III) nitrate.

A number of investigators have demonstrated that in pregnant rodents exposed to inorganic chromium only a very small fraction of the administered dose is transported to the fetus in utero. Visek et al. (1953) gave ^{51}Cr, as a single dose, in the form of sodium chromate(VI) or chromium chloride(III) intravenously to rats on days 15 to 20 of gestation. Fifty μCi per dose was administered, and specific activity ranged from 200 to 1250 μCi/mg. Litters were examined 24 hours post-injection. Regardless of chemical form or time of administration, recovery of ^{51}Cr per total litter never exceeded 0.13% of the administered dose.

Mertz et al. (1969) administered ^{51}Cr as chromium acetate(III) to rats. Single doses were given either intravenously or by gavage at mating. Repeated doses were given either by daily intubation during gestation or by administration in the drinking water, at a concentration of 2 mg/ℓ. Five μCi were given intravenously and either 5 or 250 μCi by gavage. Specific activity ranged from 30 to

100 μCi/μg. Pups were sacrificed no later than 3 hours following birth. No ^{51}Cr was detected in the young at birth following a single dose by either route to the dam at mating. Repeated dosing by gavage during gestation resulted in labeling of the litters at birth with from 0.5 to 1.5% of the mothers' total body activity. Exposure of dams via the drinking water did not result in transfer of ^{51}Cr to the litters.

Danielsson et al. (1982) found considerable differences between Cr(III) and Cr(VI) in their distribution in embryonic and fetal uptake. Forty-two pregnant mice received single doses (5 μg/kg intravenously) of $CrCl_3$ or $Na_2Cr_2O_7$ on days 8 to 18 of gestation. On day 13 of gestation, embryonic concentrations were 12% Cr(VI) and 0.4% Cr(III). Fetal concentration of both compounds increased with gestational age, probably binding to fetal calcified bone, which develops on day 14.

Iijima et al. (1983) found that radiolabeled Cr levels in fetal tissues increased, while levels in maternal blood decreased after single intraperitoneal injections of 9.8 mg Cr (as $^{51}CrCl_3$)/kg body weight.

Matsumoto et al. (1976) examined placental transfer following subcutaneous administration of $CrCl_3$(III) to ICR mice. Six control mice were injected with saline, 11 mice were injected with $CrCl_3$ (as Cr) at a dose of 9.76 mg/kg, and 6 mice were injected with 19.52 mg/kg. Mice were injected 9 times every other day from the first to the sixteenth day of gestation.

Although there appeared to be a trend of increasing chromium in the pups with dose, levels were not significantly different from controls for either dose group. The high dose dams did exhibit placental chromium concentrations that were significantly elevated above controls.

In contrast to these studies, when ^{51}Cr was administered to rats in the form of glucose tolerance factor (a low molecular weight organic complex isolated from yeast) by stomach tube during gestation, from 20 to 50% of the dam's radioactivity was detected in the litters (Mertz et al., 1969). This is consistent with the role of chromium as an essential trace element.

In conclusion, the limited data indicate that small amounts of chromium are transferred from mother to offspring. In one study, embryonic and fetal uptake of Cr(VI) was approximately 10 times higher than that of Cr(III), when both were administered at the same doses to pregnant mice. In light of the limited work that has been done in this area, it is clear that further investigation is called for, particularly with regard to uptake in the early fetus.

5.2.2. Distribution.

5.2.2.1. BLOOD -- Once absorbed, Cr(III) compounds are cleared rapidly from the blood and more slowly from the tissues. This also indicates that blood-chromium levels are inadequate indicators of body burden. Clearance of Cr(VI) from the blood is slower, presumably due to uptake by erythrocytes followed by reduction to the relatively impermeable Cr(III).

Hopkins (1965) injected 0.1 µg ^{51}Cr (as chromium chloride)/100 g intravenously in male rats. The blood chromium content as a percent of the 15 minute blood concentration at various time intervals was: 30 minutes, 94%; 1 hour, 87%; 2 hours, 69%; 4 hours, 66%; 8 hours, 47%; 24 hours, 17%; 48 hours, 9%; 96 hours, 5%. Withey (1983) replotted this on semi-log paper and resolved the curve into initial, intermediate, and terminal phases with respective half-lives of 0.56, 5.53 and 57 hours (Figure 5-1). A correlation coefficient of 0.98 was derived when these data were fit to a linear curve ($Y = a+b \ln x$).

Visek et al. (1953) compared clearance and distribution following intravenous injection of several chromium salts in rats. Four days following injection, $NaCrO_2$ (III) blood levels were <0.02% of the administered dose per gram of

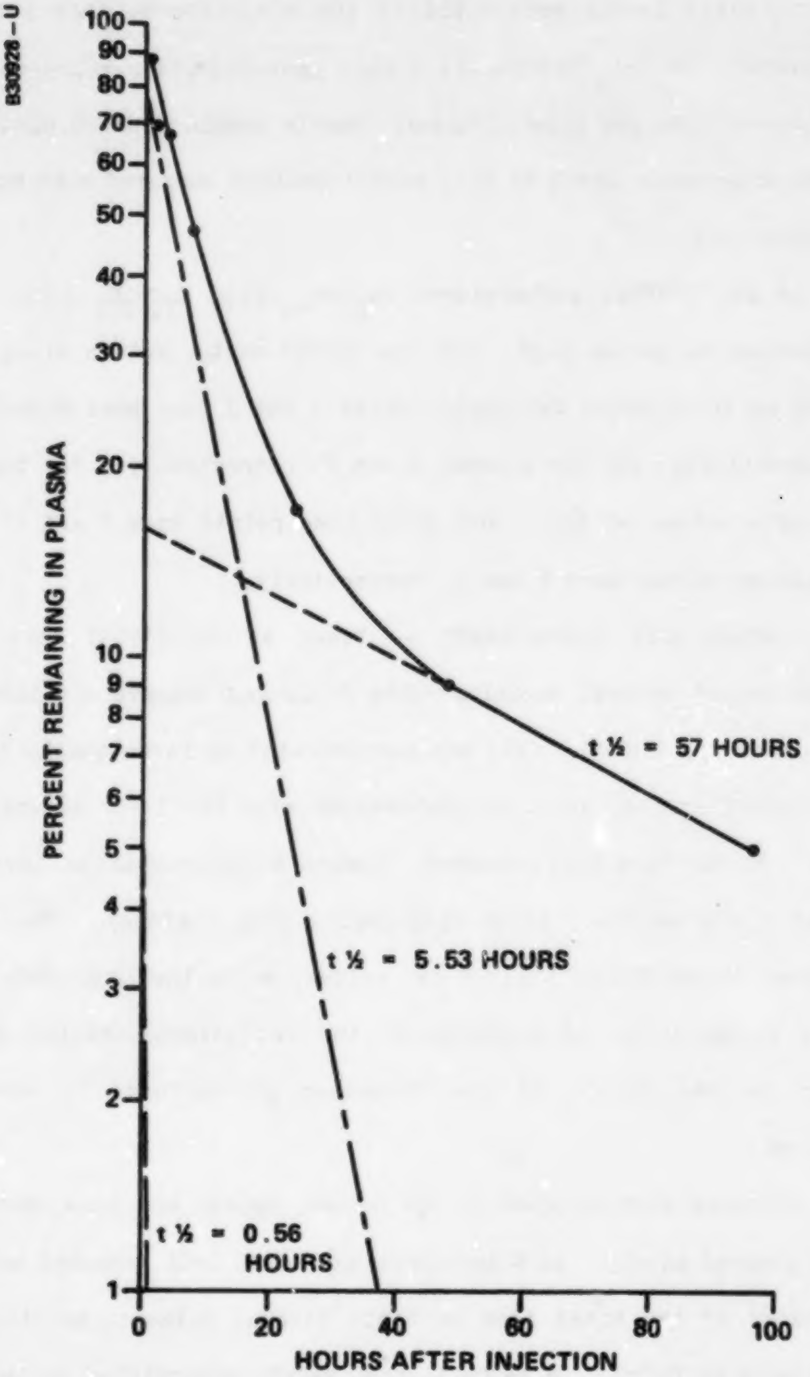

Figure 5-1. Rate of blood clearance of intravenously injected ^{51}Cr (III) from male rats. Data from Hopkins (1965) as replotted by Whithey (1983).

blood and $CrCl_3$ (III) levels were 0.05% of the administered dose per gram of blood. In contrast, Na_2CrO_4(VI) levels 4 days post-injection represented 0.52% of the administered dose per gram of blood. Nearly complete blood clearance for this salt was not achieved until 42 days post-injection compared with only 7 days for the trivalent salt.

Baetjer et al. (1959a) administered Na_2CrO_4 (VI), $K_2Cr_2O_7$ (VI), or $CrCl_3$ (III) intravenously to guinea pigs. For the Cr(VI) salts, values of μg Cr/10 gm dry tissue/200 μg Cr injected for erythrocytes 1 and 3 days post-injection were 28 and 31, respectively, and for plasma, 4 and 2, respectively. For the Cr(III) salt, erythrocyte values at the 1 and 3 day time points were 1 and <1, respectively, and plasma values were 5 and 3, respectively.

5.2.2.2. OTHER BODY COMPARTMENTS -- Visek et al. (1953) have reported organ distribution of several chromium salts following intravenous injection in rats. Sodium chromite ($NaCrO_2$) (VI) was concentrated in large quantities by the reticuloendothelial system, which in combination with the liver accumulated 90% of the dose. At 42 days post-exposure, organs with detectable levels were: spleen > liver > bone marrow > tibia epiphysis > lung > kidney. The liver and spleen contained 33 and 50% of their 4 day values, while the lung contained 10%. The extensive accumulation of chromite in the reticuloendothelial system is postulated to be the result of the formation of colloids by chromite at physiological pH.

Chromic chloride concentrated in the liver, spleen and bone marrow; once deposited, it cleared slowly. At 4 days post-exposure, $CrCl_3$ exposed animals had lower percentages of the total dose in their livers, spleens, and bone marrow than those exposed to $NaCrO_2$. More $CrCl_3$ than $NaCrO_2$ accumulated in the kidney, however. All organs gradually cleared chromite over the period of the study. In contrast, the liver in $CrCl_3$-exposed rats was the only organ to clear significant amounts of chromium over the study period (45 days).

Cr(VI) was picked up to a much smaller extent than either of the Cr(III) salts. At the 42-day time point, <1% of the dose was found in the liver. For comparison with the trivalent salts, 4-day tissue concentrations in animals given sodium chromate were (% dose/g tissue): liver, 0.52%; spleen, 0.91%; bone marrow, 0.56%; tibia epiphysis, 0.38%. At 42 days, corresponding values were: liver, 0.07%; spleen, 4.8%; bone marrow, 0.16%; tibia epiphysis, <0.02%. The increase in spleen concentration was attributed to erythrocyte destruction.

Hopkins (1965) examined the kinetics of distribution with trace quantities of chromic chloride in the rat. Measured concentrations at 15 minutes post-injection were highest in lung and kidney, followed by heart, pancreas, liver, bone marrow, spleen, testis, and brain. The heart, lung, pancreas, liver, and brain showed maximal levels at this 15-minute time point, and subsequently declined. The spleen reached a maximum level 96 hours post-exposure and the testis 4 hours post-exposure (300 times the initial level), while the kidney concentration remained unchanged over 96 hours.

Following intratracheal administration of chromate to rats, highest concentrations were found in the lung, followed by liver, kidney, and spleen (Baetjer et al., 1959a). In contrast to the injection studies, significant concentrations were not found in bone.

Following a single oral dose of chromate administered by gavage, highest concentrations were found in the liver, followed by the kidney and the spleen (MacKenzie et al., 1959). When chromate was administered in the drinking water for 1 year, highest concentrations were found in the spleen, followed by the kidney, liver, and bone. Year long administration of chromic chloride resulted in the same type of distribution pattern with lower absolute quantities.

Generalizations regarding the behavior of the two valence states are difficult to make, since almost all testing has involved chromic chloride(III) and sodium chromate(VI) or potassium dichromate(VI). The data of Visek et al. (1953) showed differences in uptake and distribution between chromic chloride and chromite; the behavior of other Cr(III) salts is difficult to anticipate. Data from chromium chloride(III) do indicate that once absorbed, this salt is quickly cleared from the bloodstream and has a long tissue residence time. Cr(VI) salts have longer residence times in the blood and are more rapidly cleared from the tissues. Comparisons of tissue distributions are difficult, because different authors choose different organs to examine and time between exposure and analysis varied considerably. In almost all instances, the following organs accumulated significant amounts of chromium: liver, kidney, spleen, and bone marrow. In addition, there are some data which indicate that the testis, heart, lung, and brain accumulate considerable amounts. Tissue distribution does not appear to be affected by the sex of the animal or by dietary history in terms of chromium content.

In humans, Teraoka (1981) studied the distribution of 24 elements in 12 Japanese males. The samples obtained at autopsy were from seven workers exposed to heavy metals and five subjects with no undue exposure. Although absolute concentrations of chromium varied extensively between individuals, the greatest concentrations of chromium were found in the Hilar lymph nodes and lungs followed by spleen, liver, kidney, and heart which all contained approximately the same level for each individual. The distribution patterns were similar for the seven men occupationally exposed to metals and the unexposed control group. The average level of chromium in the Hilar lymph nodes of unexposed men was 8.2 ppm as compared with 2400 ppm for the two chromium plating workers and 152 ppm for the three chromate refinery workers. An airplane painter and stone mason who had possible exposure to chromium had levels of 33 and 4.2 ppm, respectively. The order of organ distribution appeared to be similar regardless of whether the exposure to chromium was from occupational (high levels) or environmental (low levels) sources.

Similarly, the highest levels of chromium were detected at autopsy in the lungs of a worker who died of respiratory cancer 10 years after retiring from a chromate manufacturing plant (Hyodo et al., 1980). The chromium levels in different portions of the lungs of this worker varied from 616 to 7100 ng Cr/g wet weight as compared to values of 19.3 to 881 ng Cr/g wet weight of similar lung sections from five control subjects. The suprarenal gland, brain, and skin also had relatively high levels of chromium as compared to the control values. It was reported that Cr(VI) was more prevalent in the chromate worker; however, the wet oxidation method, using hot nitric acid and perchloric acid, has the potential of oxidizing Cr(III) to Cr(VI) and makes these results invalid.

Lim et al. (1983) conducted a study of radiolabeled Cr kinetics in three normal and three hemochromatotic patients used in a previous study. After intravenous injection of ^{51}Cr(III), absorption and distribution were determined with a whole body gamma-ray scintillation scanner, whole body counts and plasma clearance determinations. Among all body organs studies, the liver and spleen contained the highest levels. In fact, after 3 months the liver contained half of the total body burden of chromium. For the liver, spleen and thigh, there were three major accumulation and clearance components, grouped in ranges of half-lives of 0.5 to 12 hour (fast), 1 to 14 days (medium) and 3 to 12 months (slow). More than 50% of the blood plasma of chromium was absorbed within hours of administration. On the basis of this study, a model was constructed in the form of a plasma pool in equilibrium with the three compartments. The fast compartment occurred in adipose and muscle tissues; the middle compartment was distributed equally between adipose and muscle tissues, and the liver and spleen; the liver and spleen composed the slow compartment.

5.2.3. Elimination. Hopkins (1965) examined the kinetics of single doses of 0.1 or 0.01 μg Cr administered intravenously as $^{51}CrCr_3$. Urinary excretion was followed over 4 days, and an inspection of a semi-log plot of these data indicated at least two elimination components, the first representing rapid blood clearance of chromium and the second the slower elimination from soft tissues. Hopkins data also indicate that, although the urine is the primary route of excretion, the intestines also play a small role.

Mertz et al. (1965) followed the elimination of single doses of intravenously administered chromic chloride over a longer time period (72 days). Whole body retention of chromium as a funtion of time was represented by a polynomial with three distinct regression terms (Figure 5-2). This evidence supports a three compartment elimination process. The half-lives for chromium in the three compartments were estimated from clearance rates to be 0.5 days, 5.9 days, and 83.4 days. At the end of 72 days, 13.5% of the original dose was retained.

Onkelinx (1977) also followed elimination of an intravenous dose of chromic chloride. Their data agree with Mertz et al. (1965), in that the plasma disappearance curve could be described by the sum of three exponential components, representing three compartments. Excretion has been quantified and 3 components have been identified. Urinary excretion represented 51 to 64% of the total excretion, fecal excretion 5 to 8%, and clearance of chromium into a body "sink" 31 to 41%. The sink represents compartments with extremely long half-lives.

In a comparison of Cr(VI) and Cr(III) elimination in rats, Sayoto et al. (1980) administered radiolabeled Na_2CrO_4 or $CrCl_3$ to animals either by intubation or intravenous injection. Regardless of the route of administration, the Cr(VI) compound was excreted more rapidly through the feces and urine. The

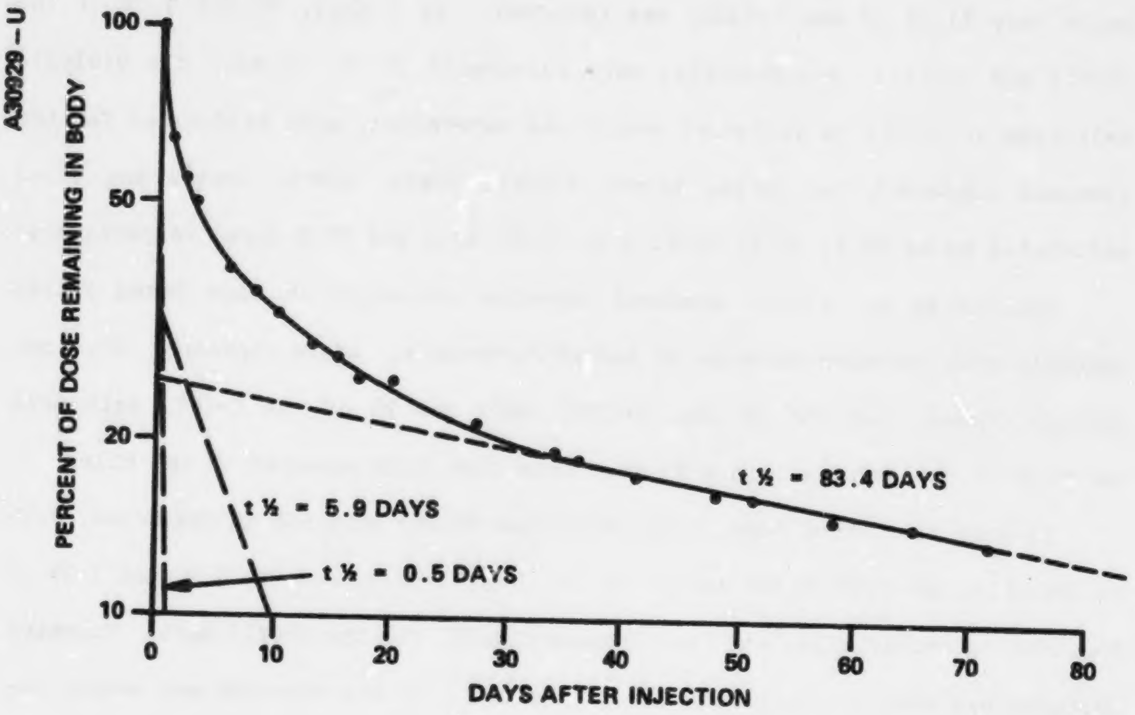

Figure 5-2 Whole-body elimination of intravenously administered ^{51}Cr (III) in male rats (Mertz et al., 1965).

biologic half life for Na_2CrO_4 and $CrCl_3$ after intubation was 22.24 and 91.79 days, respectively. The authors suggested that these findings indicated that Cr(III) has a higher affinity for body constituents than Cr(VI).

Yamaguchi et al. (1983) studied the excretion of a Cr(III) and Cr(VI) following subcutaneous administration to rats of $Cr(NO_3)_3$ and $K_2Cr_2O_7$. Within 24 hours after treatment 93.6% of the Cr(VI) was removed from the site of injection while only 21.3% of the Cr(III) was adsorbed. In 7 days, 48 and 8.0% of the Cr(VI) and Cr(III), respectively, were eliminated in the urine. The biologic half-time of Cr(VI) in different organs was determined, with half-times for the terminal component for lungs, liver, kidney, brain, heart, testes and blood calculated to be 20.9, 15.7, 10.5, 9.6, 13.9, 12.9 and 13.9 days, respectively.

Collins et al. (1961) examined chromium excretion in dogs dosed intravenously with chromium chloride or sodium dichromate. Acute exposures (dose not stated) showed that 25% of the Cr(III) salt and 9% of the Cr(VI) salt were excreted in the urine within 4 hours. Less than 0.5% appeared in the bile.

In bile fistulated dogs, 4-day excretion values were 50% in the urine, 0.5% in the bile, and 3.7% in the feces for the Cr(III) salt, and 20, 0.9, and 1.2% of the dose in urine, bile, and feces, respectively, for the Cr(VI) salt. Excreted chromium was readily dialyzable indicating that, if the chromium was bound, the molecule it was combined with was of small size or the binding was reversible. Tubular reabsorption appeared to represent $\geq$63% of the amount filtered.

Davidson et al. (1974) examined kidney handling of chromium in normal human subjects and in dogs (not pre-treated with chromium). Their results indicate that in both dogs and man physiological quantities of chromium have a >99% reabsorption value. Their data also suggest that there is an active transport mechanism in the renal tubule for chromium reabsorption. They hypothesize that the normal filtered load for chromium may be close to the maximal reabsorption rate. If this is the case, then any increase in plasma chromium concentration would result in a significant increase in renal excretion of chromium.

Cikrt and Benco (1979) measured the excretion of ^{51}Cr in urine, bile and feces of rats within 24 hours after intravenous injection of $CrCl_3$ or Na_2CrO_4(3μmol/kg). ^{51}Cr excretion in urine (as a fraction of the dose) averaged 22.4 ± 2.8% for Cr(VI); ^{51}Cr excretion in bile averaged 0.5 ± 0.1% for Cr(III) and 3.5 ± 0.7% for Cr(VI); and ^{51}Cr excretion in feces (including gastrointestinal contents) averaged 4.2 ± 0.2% for Cr(III) and 7.4 ± 0.4% for Cr(VI). These measurements indicate that urinary excretion of CR(III) and Cr(VI) are equivalent, but biliary excretion of Cr(VI) averages 7-fold that of Cr(III) under the same conditions.

Norseth et al. (1982) administered $^{51}CrCl^3$ and $Na_2{}^{51}CrO_4$ to rats by intravenous injection (1-9 μmol/kg) and identified ^{51}Cr(III)-glutathione complexes in bile after the administration of both compounds. They also demonstrated that biliary excretion of the Cr-glutathione complex is inhibited by diethylmaleate. This experiment furnishes important evidence that glutathione is involved in the biliary excretion of chromium. Yamamoto et al. (1982) isolated a low-molecular-weight, chromium-binding constituent in liver and kidney cytosol of mice treated with Cr(VI); the low-molecular-weight chromium constituent was also detected in urine and feces. Alexander et al. (1982) showed that rat liver mitochondria accumulated Cr(VI) fairly rapidly, although the relative uptake decreased with increasing dose. Trivalent chromium was taken up at a much lower rate than hexavalent chromium.

5.3. SUMMARY

There are increasing experimental data available on the pharmacokinetics of chromium. Absorption by inhalation exposure appears to occur rapidly, although it is difficult to quantify the extent of absorption. A preliminary estimate of pulmonary absorption, following disposition of $CrCl_3$ into the lungs by instillation, indicates that approximately 5% is absorbed. Following oral exposure, gastrointestinal absorption was also low with estimates that only 5% or less of chromium was absorbed. In vitro studies indicate that gastrointestinal juices have the capability to reduce Cr(VI) to Cr(III); however, there are insufficient data from in vivo studies to demonstrate whether this reduction process has the capacity to eliminate any differences in absorption between ingested Cr(VI) and Cr(III) compounds. Percutaneous absorption of chromium through unbroken skin is variable and dependent on valence as well as the specific salt.

After absorption, chromium is transported by the blood with Cr(III) transport facilitated by specific binding proteins in the blood. Cr(VI) on entering the blood stream diffuses into the blood cells where reduction and binding to cellular components occurs. Both absorbed Cr(III) and (VI) can be transported to a limited extent to the fetus in utero after exposures of the dams, although the data do not allow quantitative estimates of fetal exposure. Chromium transported by the blood is distributed to other organs with greatest retention by the spleen, liver, and bone marrow. The major deposition site following inhalation exposure is the lungs, where chromium probably binds to the cellular material before absorption can occur.

Absorbed chromium is eliminated from the body in a rapid phase representing clearance from the blood and in a slower phase representing clearance from tissues. Urinary excretion is the primary route of elimination accounting for somewhat over 50% of the eliminated chromium, while fecal excretion accounts for only 5% of the elimination from the blood. The remaining chromium is deposited into deep body compartments. Limited work on modeling the absorption and deposition of chromium indicates that adipose and muscle tissue retains chromium at a moderate level (≈2 weeks), while the liver and spleen store chromium for up to 12 months. Estimated half-lives for whole body chromium elimination are 22 and 92 days for Cr(VI) and Cr(III), respectively.

6. CHROMIUM AS AN ESSENTIAL ELEMENT

6.1. CHROMIUM DEFIENCY

The nutritional need for chromium as an essential element has been reviewed by Golden and Golden (1981), Anderson (1981), Saner (1980) and Mertz (1974). Mertz (1974) described the necessary components for considering an element as essential. These components are: the element must be found in living matter, the element must interact with living biological systems, and deficiency of the element must produce a decrement in biological function. Indeed, certain chromium compounds are found in living matter, it does interact with living systems, and deficiency syndromes are remedied with its supplementation.

The National Academy of Science (NAS, 1980) has summarized daily intakes of chromium by persons in the United States as: dietary, a range of 37 to 130 μg/day with an average of 62 μg/day; air, a range of <0.5 to <4.0 of the dietary intake; and drinking water, a range of 0 to 224 μg/day with an average of 17 μg/day. Mertz (1974) provided similar estimates that daily intake of chromium in healthy humans was between 5 and 100 μg/day and that this intake resulted in blood and urine levels of chromium of 0.5 to 5 and 5 to 10 μg/ℓ, respectively. Infants receive chromium through breast milk during nursing (Kumpulainen et al., (1980). These levels of chromium intake must be adequate since no serious effects from chromium deficiency have been observed in the general populace. The Estimated Adequate and Safe Intake (EASI) values for chromium, provided by the National Academy of Science (NAS, 1980), are listed in Table 6-1. The lower EASI values are based on the average United States daily intake from a mixed diet. No Recommended Daily Allowance (RDA) has been issued.

TABLE 6-1

Estimated Adequate and Safe Intake (EASI) for Chromium*

	Age (years)	EASI (mg/day)
Infants	0.0 to 0.5	0.01 to 0.04
	0.5 to 1.0	0.02 to 0.06
Children	1 to 3	0.02 to 0.08
	4 to 6	0.03 to 0.12
	7 to 10	0.05 to 0.20
	≥11	0.05 to 0.20
Adults		0.05 to 0.20

*Source: NAS, 1980

Animal studies have been conducted to determine the effects of ingestion of dietary chromium. Schroeder et al. (1964) maintained 54 male and 54 female mice for life on drinking water containing 5 ppm of Cr(III). The mice exposed to chromium had survival rates similar to those of control animals and mean body weights that were 123% of control values. In this study the food was devoid of all trace metals. In an identical study using groups of 50 male and female Long-Evans rats, Schroeder et al. (1965) observed increased longevity in the treated animals. In studies of the effects of the absence of chromium in the diet, Roginski and Mertz (1969) raised rats in plastic cages on low protein diets containing less than 100 ppb Cr(III). A second group of rats were given a chromium supplement of 2 ppm Cr(III) in the drinking water. The chromium supplemented rats had better weight gain than the chromium deficient animals. This difference in weight gain was more striking if the animals were allowed free access to an exercise wheel. When extreme care was taken to also prevent airborne exposure to chromium of rats maintained on chromium deficient diets, there was a high incidence of moderate hyperglycemia and glycosuria as compared to animals on chromium supplemented diets. These studies suggest that small amounts of dietary Cr(III) were beneficial to the health of these rats. Preston et al. (1976) maintained female guinea pigs on low protein diets containing 0.125, 0.5, or 50 ppm chromium along with adequate levels of vitamins and some other trace metals. After 8 to 13 weeks of maintenance on these diets, the animals were mated and allowed to deliver pups. Although the diets had no effect on the survival of animals not mated, there was a significant decrease in survival of mated animals on the low chromium diet (13 of 24 animals died) as compared to animals on the low chromium supplemented diet (4 of 24 animals died) and the high chromium supplemented diet (3 of 24 animals died). It was suggested that the added stress of mating and pregnancy along with chromium deficiency resulted in the high level of mortality. Other parameters examined included weight gain and glucose loading; serum cholesterol levels were not altered by dietary chromium. It was concluded that chromium was beneficial to survival in guinea pigs as was previously reported for mice and rats.

6.2. GLUCOSE TOLERANCE FACTOR

Chromium deficiency in the diet results in glucose intolerance in both the experimental animals and humans (Saner, 1980). Schwarz and Mertz (1959) have identified a glucose tolerance factor (GTF) which was required in rats to maintain normal rates of glucose removal from the blood stream. This factor has been obtained from natural sources including brewer's yeast and hydrolyzed pork kidney. In further studies, Mertz and Schwarz (1959) demonstrated that rats maintained on some commercial diets had normal glucose removal rates, while maintenance on other diets resulted in poor removal of glucose from the blood. When the second diets were supplemented with GTF, glucose removal rates returned to normal values. Mertz and Schwarz (1959) have identified Cr(III) as the active agent in the GTF. It was further demonstrated that administration of a variety of Cr(III) compounds to glucose intolerant rats resulted in an increase in the rate of removal of glucose from the blood. In this assay, the less stable Cr(III) compounds were most effective, and some Cr(VI) compounds were totally without activity.

The effects of chromium on glucose metabolism were suggested to result from chromium being a co-factor for insulin. Mertz et al. (1965) measured insulin stimulated CO_2 production in adipose tissue from chromium deficient rats receiving supplements of 0.0, 0.01, 0.05, or 0.1 µg Cr/100 g body weight. The adipose tissue of rats receiving 0.05 µg Cr/100 g produced significantly more

CO_2 than tissues obtained from other groups. Farkas and Roberson (1965) performed similar studies with measurements of glucose utilization in rat lenses taken from animals on chromium deficient and supplemented diets. The chromium treatment alone did not affect glucose utilization; however, chromium treatment in conjunction with insulin significantly increased the utilization of glucose. Administration of 2 ppm of chromium in the drinking water of rats also facilitated the insulin transport of amino acids into the heart and the incorporation of amino acids into protein. Providing chromium supplements to rats increased the animals' sensitivity to many of the effects of insulin.

Saner (1980) states that certain groups of persons may be prone to chromium deficiency; these groups include the elderly, diabetics, pregnant women, malnourished children, offspring and siblings of diabetics, persons with early coronary heart disease and their offspring. Jeejeebhoy et al. (1977) have described a female patient placed on total parenteral nutrition for 3 1/2 years in whom chromium deficiency was indicated. Blood chromium levels were reported as 0.55 ng/mℓ and hair chromium levels as 154 to 175 ng/gm. In addition to glucose intolerance, weight loss, neuropathy, elevated fatty acid levels, reduced respiratory quotient, and abnormal nitrogen metabolism were reported. Daily administration of 250 μg chromium chloride for 2 weeks in the parenteral infusate, followed by 20 μg/day maintenance, resulted in a reversal of symptoms. Freund et al. (1979) report similar finding of chromium deficiency in a patient receiving total parenteral nutrition. Supplementation of the infusate with 150 μg chromium/day resulted in the reversal of the adverse clinical findings of impaired glucose tolerance, weight loss, and confusion.

Chromium has been known to affect glucose tolerance in humans. Levin et al. (1968) performed oral glucose tolerance tests on 9 male and 6 female elderly subjects. Of the subjects tested, 10 daily dietary supplements with 150 μg/day chromium for 3 to 4 months resulted in normal glucose tolerance in four subjects. The remaining six subjects still had abnormal tests after receiving the chromium supplement. Glinsmann and Mertz (1966) observed improved glucose tolerance in three of six diabetics given 150 to 1000 µg of Cr(III) for 15 to 120 days. In a similar study, Sherman et al. (1968) observed no change in the glucose tolerance of ten diabetics who received chromium supplements of 100 µg/day for 16 weeks. In malnourished infants, Gurson and Saner (1971) and Hopkins et al. (1968) observed dramatic increases in glucose removal and utilization following treatment with Cr(III). To ensure that the improved glucose tolerance was the result of chromium therapy, Hopkins et al. (1968) treated five infants in a manner similar to the others with the exception that chromium was not administered. These five infants showed no improvement in glucose tolerance. Dieatary chromium appears to have some effect on human glucose tolerance; however, the therapeutic effect of chromium supplementation on subjects with abnormal glucose tolerance was variable.

6.3. SUMMARY

Animal studies have demonstrated that chromium deficient rodents gain less weight and have a shorter lifespan than animals maintained on a diet containing adequate chromium levels. Chromium deficiency results in glucose intolerance in rats and this intolerance can be reversed by dietary treatment with Cr(III). More effective in reversing glucose intolerance is a chromium complex which has been isolated from brewer's yeast and designated as glucose tolerance factor (GTF). GTF may be formed in mammals following ingestion of inorganic chromium. Some humans with abnormal glucose tolerance, such as the elderly, diabetics, and malnourished infants have responded to dietary supplements of chromium.

Although the exact level of chromium needed for good health is not known, it is assumed from the lack of observed effects of chromium deficiency that the average American intake of 0.05 to 0.2 mg/day is adequate. It is also worth noting that there is a considerable difference between the low levels of chromium intake that are associated with nutritional deficiency, and those discussed in the following Chapter 7 which have been associated with toxic effects.

7. CHROMIUM TOXICOLOGY

7.1. ACUTE EFFECTS OF CHROMIUM EXPOSURE IN MAN AND ANIMALS

7.1.1. Human Studies. Chromium metal is biologically inert and has not been reported to produce toxic or other harmful effects in man. When in contact with the skin, compounds of chromium in the trivalent state combine with proteins in the superficial layers, but do not cause ulceration (NAS, 1974).

Cr(VI) compounds are responsible for the majority of the health problems associated with all chromium compounds. They are irritating and corrosive, and may be absorbed by inhalation, cutaneously, or by ingestion. Acute systemic poisoning is rare; however, it may follow deliberate or accidental ingestion or result from absorption through broken skin (NAS, 1974).

Much of the information on the effects of Cr(VI) is obtained from occupational exposures, where the predominant exposures and related effects are on the respiratory system and skin (NAS, 1974). As with most information derived from uncontrolled settings, exact knowledge about length of exposure, concentration of the chemical, and other variables are not known, making quantitive dose-effect relationships difficult.

7.1.2. Animal Studies. Cr(III) compounds have a very low order of toxicity when administered orally. Oral LD_{50} values for the rat have been reported as follows: chromic chloride, 1.87 g/kg; chromium acetate, 11.26 g/kg; chromium nitrate, 3.25 g/kg (Smyth et al., 1969). Kobayashi et al. (1976) have determined oral LD_{50} for chromium trioxide in mice and rats to be 135 to 177 mg/kg and 80 to 114 mg/kg, respectively, with death occurring between 3 to 35 hours.

Symptomatology included diarrhea, cyanosis, tail necrosis, and gastric ulcer. Surviving animals showed increases in liver and testes weight without microscopic changes.

Cr(VI) is more acutely toxic than Cr(III). A primary effect of acute exposures is kidney failure. Oral administration of high doses results in gastric corrosion. The oral LD_{50} of sodium dichromate in humans has been reported as 50 mg/kg (NIOSH, 1979).

Kidney effects are the primary result of acute exposures to chromium by various routes. Relevant studies are summarized in the following paragraphs.

Mathur et al. (1977) injected rabbits intraperitoneally with 2 mg/kg chromium nitrate or potassium chromate daily for 3 or 6 weeks. After 3 weeks of exposure, kidneys from animals dosed with chromium nitrate showed marked congestion, extravasation of red blood cells in the intratubular spaces and tubular necrosis. Further treatment for 6 weeks did not produce additional changes.

The kidneys from animals given potassium dichromate showed marked congestion, and the walls of the small blood vessels were thickened. Glomerular tufts were shrunken in some places, while proliferation of endothelial cells, obliterating the Bowman space, was seen in others. There was necrosis and desquamation of the epithelium of the convoluted tubules. Red blood cells were found in the intertubular spaces. Changes were similar whether animals were exposed for 3 or 6 weeks.

Hunter and Roberts (1933) dosed monkeys subcutaneously with 1 to 5 mℓ of a 2% solution of potassium dichromate over a 5-week period. One monkey died following the final dose. The authors reported injury to the proximal and distal convoluted tubules and the glomeruli of the kidneys.

Kirschbaum et al. (1981) injected rats subcutaneously with 20 mg/kg sodium chromate. Epithelial cell injury in the kidney occurred 2 to 4 hours post-injection. They postulated that the interaction of chromium with specific elements of the microfilamentous system, which are responsible for directing intracellular flow of reabsorbed solutes, may be the initial effect of chromium nephropathy. Baines (1965) also reports renal damage following exposure of rats to acute, subcutaneous doses of potassium dichromate.

Evan and Dail (1974) also report data which indicate effects on the proximal convoluted tubules following intraperitoneal administration of 10 or 20 mg/kg sodium chromate and the formation of large lysosomal vacuoles in this region. They also report effects on mitochondrial configuration shortly following exposure.

Berndt (1976) reports in vitro data which indicate there may be species differences in kidney susceptibility to chromium nephropathy. In kidney slices from rats, effects were independent of valence state. Kidney slices from rabbits were more sensitive to transport process inhibition by Cr(VI).

Mathur et al. (1977) documented effects in other target organs following acute exposure to chromium. Rabbits were dosed intraperitoneally with 2 mg/kg chromium as chromium nitrate or as potassium dichromate. Doses were given daily and the animals were sacrificed after 3 or 6 weeks. Administration of Cr(III) for 3 weeks produced changes in the brain, including occasional neuronal degeneration in the cerebral cortex, marked chromatolysis, and nuclear changes in the neurones. Six weeks of exposure resulted in marked neuronal degeneration in the cerebral cortex accompanied by neuronophagia, neuroglial proliferation, and meningeal congestion.

Following 3 weeks of exposure to Cr(VI), congestion with perivascular infiltration by inflammatory cells was noted. In addition, some neurones in the cortex showed pyknotic nuclei and dissolution of Nissl's substance. Neuronophagia and focal neuroglial profileration were also evident throughout the cerebral cortex. Changes following 6 weeks of exposure were similar. The myocardium of animals exposed to Cr(III) for 3 weeks appeared to be normal. However, following 6 weeks of exposure, the myocardium showed marked congestion and degeneration of muscle fibers. Exposure to Cr(VI) for 3 weeks did not produce any abnormalities. Exposure for 6 weeks produced changes similar to those seen in animals exposed to the trivalent salt.

Tandon et al. (1978) report hepatic changes in rabbits exposed to chromium. Exposure conditions were the same as in the previous study. Exposure to Cr(III) for 3 weeks produced marked congestion and dilation of the central veins and sinusoids. Discrete foci of necrosis were noted in liver parenchyma. After 6 weeks, in addition to marked congestion, extensive hemorrhage was seen in the parenchyma. Slight nuclear pleomorphism and multinucleated cells were noted in the lobules. Bile duct proliferation, increased cellularity and proliferation of fibroblasts around portal tracts were noted.

Exposure to Cr(VI) for 3 weeks produced more extensive pathology than did Cr(III) exposure. The liver capsule was thickened and there was marked congestion of central veins and adjacent sinusoids. Large areas of necrosis were seen throughout the parenchyma. Changes seen following 6 weeks of exposure were similar to those described following 6 weeks of exposure to the trivalent salt.

In summary, the kidney appears to be the main target for acute chromium toxicity, with effects occurring at 1-2 mg Cr(VI)/kg body weight. Although hepatic effects have also been observed, the kidney has received the most intense study.

7.1.3. Chromium Hypersensitivity.

7.1.3.1. CHROMIUM SENSITIVITY AND CONTACT DERMATITIS -- Chromic acid and the chromates are powerful skin irritants, and, in lower concentrations, the chromates are sensitizers (NAS, 1974). Workmen exposed to the steam of boiling dichromate solutions developed an acute primary irritant contact dermatitis (Schwartz et al., 1957; White, 1934). White (1934) described a diffuse erythematous dermatosis that resulted from dichromate; some progressed to an exudative phase.

Various chromium compounds have been implicated in giving rise to allergic dermatitis with varying degrees of eczema. Parkhurst (1925) reported the case of a woman employed in blueprint production using a process in which a 1% potassium dichromate solution was used as a fixative. A 0.5% potassium dichromate solution was rubbed on the right thigh of the woman, and soom after the application, there was a local sensation of itching and burning. Twelve hours later, the patient developed a follicular erythematopapular dermatitis at the exposure site. Itching and burning was reported when a similar application was made to the left thigh.

Smith (1931) reported a case of chromium sensitization in a man who had been hospitalized after occupational exposure to ammonium dichromate. The patient had ulcerations in the skin of both hands, and complained of asthma, and muscular weakness and tenderness. He had a previous history of asthma and hay fever and had further asthmatic attacks upon exposure to chromium. Following a patch test with 1% ammonium dichromate solution on a 1 cm^2 area of normal skin on his forearm, the man developed a mild erythema after 24 hours. After 3 days, the erythematous area doubled in size, and there was the appearance of vesicles. An intradermal injection of 0.1 mℓ of a 0.5% aqueous solution of ammonium dichromate was given in the right forearm 8 days later. Within an hour, the patient developed a generalized pruritis with soreness at the injection site. This progressed with the development of a vesicular erythematous dermatitis covering the entire hands and lower parts of the forearm. In addition, he developed diaphoresis and sibilant rales. These symptoms which required hospitilization abated after his exposure to Cr(VI) ceased. Three control subjects who were similarly injected showed no reaction.

Hall (1944) reported on 132 aircraft workers who developed dermatitis after contact with a primer consisting of a suspension of zinc chromate powder and magnesium silicate in a xylene solution of certain resins, including a phenol-formaldehyde resin. Those workers who had dermatitis from the primer and who were allergic to zinc chromate pigment had a mean duration of employment of 7 months (range: 1 week to 9 years). A battery of patch tests showed that 90 of the workers (68%) were sensitive to the zinc chromate pigment only. (Apparently, the zinc chromate pigment was a mixture of zinc chromate and calcium carbonate.) Only a few workers had positive patch tests for other compounds encountered on the job.

Forty-five cases of allergic contact dermatitis, observed in the Helsinki area from 1945 to 1948, were reported by Pirila and Kilpio (1949). Positive patch-testing with a 0.5% aqueous solution of potassium dichromate (pH 4.15) was observed in 41 of the workers. The workers were involved in the following occupations: 11 bookworkers, 10 cement and lime workers, 7 radio factory workers using a photostatic procedure, 4 metal factory workers, 4 painters and polishers, 3 fur workers, and 6 others.

Engebrigsten (1952) reported eight cases of cement eczema among 300 to 400 Norwegian workers exposed "more or less directly" to cement dust that contained 0.002 to 0.020% water-soluble Cr(VI), which was described only as "water-soluble chromates." Positive patch testing was reported in 7 of 8 patients exposed to 0.5% aqueous solution of potassium dichromate. Positive reactions to cement patch tests were observed in 4 of 8 patients. Of the 10 persons who served as controls, none gave any positive reactions. Engebrigtsen (1952) subsequently tested the same eight patients with a cement slurry that had been washed free of Cr(VI), and none of the people reacted positively.

Denton et al. (1954) patch tested a patient with a "strong specific hypersensitivity to potassium chromate" with three solutions: (1) a 50 ppm solution of potassium dichromate, (2) 1 ppm water-soluble Cr(VI) filtrate from American portland cement, and (3) 4 ppm water-soluble Cr(VI) filtrate from American portland cement. Each patch test resulted in an erythematous, edematous, and papulovesicular reaction. There was no reaction to distilled water and none of the control subjects reacted to any of the three Cr(VI) solutions.

Six out of 200 employees who worked in a diesel locomotive repair shop were incapacitated by chromate dermatitis (Winston and Walsh, 1951). All were exposed to an alkaline diesel locomotive radiator fluid that contained 0.08% sodium dichromate. Positive patch testing was reported for both sodium dichromate (pH 4.25) and the radiator fluid (pH 10).

Walsh (1953), in a summary report on chromate hazards in industry, described the following patch test results: 2% "chromate acid" applied for 24 hours on superficial skin abrasions produced a crusted lesion in 3 weeks; 0.5% sodium dichromate, reapplied daily for 3 days, produced a crusted lesion in 3 weeks; 0.5% potassium chromate, applied 8 hours/day for 3 days, produced lesions in 3 days; 0.5% sodium chromate, 0.005% sodium dichromate, and pure zinc chromate also produced lesions in 3 days after being in contact with skin for 8 hours/day for 3 days. Lead chromate did not produce a reaction after the same exposure period. A 10% solution of Cr(III) nitrate produced redness after the solution was reapplied daily for 3 days.

Edmundson (1951) obtained only two positive reactions with patch testing in 56 men who had chrome ulcers. All men were said to have a history of chrome dermatitis. He concluded that the presence of chrome ulcers did not necessarily indicate sensitization.

Other investigators (Morris, 1955; McCord et al., 1931; Levin et al., 1959) have demonstrated sensitization to other chromium compounds in workers employed as tanners and lithographers. Many of the workers gave positive results for patch tests.

There have been numerous case reports of contact dermatitis resulting from exposure to a variety of chromium-containing products, such as matches, automobile primer paint, and fumes from welding rods (Fregert, 1961; Engle and Calnan, 1963; Newhouse, 1963; Fregert and Ovrum, 1963; Shelley, 1964). In most of these reports, the subjects developed a positive reaction to patch testing for a solution of potassium dichromate.

A study conducted in France by Jaeger and Pelloni (1950) demonstrated that workers with cement eczema were sensitive to potassium dichromate. In their study, the authors patch tested 32 patients with cement eczema and 168 patients with eczema from other causes. Those with cement eczema gave positive patch tests (94%) to an aqueous 0.5% solution of potassium dichromate, while only 5% of the other eczema patients exhibited positive reactions from the dichromate.

However, Perone et al. (1974) reported that only 2 of 95 construction workers who regularly worked with cement gave a positive reaction to patch testing to a solution of 0.25% potassium dichromate or a solution containing 450 ng/g Cr(VI) extracted from cement. The authors suggested that the cement dermatitis present in the construction workers was associated with the initiative nature of the cement rather than a hypersensitivity.

There have been two reported cases of eczema in men who regularly worked with cement and who each had a green tattoo which contained chromium (Cairns and Calnan, 1962; Loewenthal, 1960). Both men developed a positive reaction to patch testing to a solution of potassium dichromate (concentration range: 0.1 to 2%). Negative results following patch testing were observed when the solution was

Cr(III) sulfate. The green pigment in one of the tatoos contained Cr(VI), but the oxidation state of chromium in the other tattoo was not determined.

Krishna et al. (1976) reported that chrome workers exposed to 0.21 to 0.80 mg/m^3 Cr(VI) displayed various dermatologic disorders, including skin ulcers, dermatitis, and nasal perforations. Dermatologic irritation has been reported by Clausen and Rastogi (1977), in auto workshop employees exposed to 0.01 to 3.75 $\mu g/m^3$; by Tandon et al. (1977), in electroplaters, polishers, and pigment workers; and by Spruit and Martin (1975), in offset printing employees who came in contact with materials (usually inks) containing up to 60,000 ppm chromium. Peltonen and Fraki (1983) found that in a population of 822 healthy volunteers, 2% of 410 men and 1.5% of 412 women showed a patch-positive test reaction to 0.5% $K_2Cr_2O_7$ solution. Most of the reactions occurred among workers in the printing industry.

Various dermatologic disorders among workers exposed to 0.001 to 0.020 mg Cr/m^3 in air and chromium on work surfaces have been reported by Lucas and Kramkowski (1975). Chromium-induced dermatitis or eczema has been associated with workers having contact with various chromium-containing lubricants and oils (Rosensteel and Lucas, 1975; Weisenberger, 1976; Clausen and Rastogi, 1977). Dermatitis associated with various chromium pigments and coloring agents has been described by Somov et al. (1976), Fisher (1977), Fregert and Gruvberger (1976), Venediktova and Gudina (1976), and Evans (1977a,b,c).

Allergic sensitization to chromium-containing compounds has been reported by Burry and Kirk (1975) in several industrially exposed individuals, and by Wahlberg and Wennersten (1977) and Kaaber and Deien (1977), who used potassium dichromate in the patch tests. Husain (1977) showed sensitization in the "general population" (not occupationally exposed), where, among 1312 patients tested, 11.58% had contact sensitivity to 0.5% potassium dichromate in a patch test (15.59% of the males reacted to the chromate as opposed to 8.18% of females tested).

Perisic and Jovovic (1977) have identified allergic contact sensitivity to chromates among 219 Yugoslavian housewives. The incidence of allergic contact sensitivity was confirmed in 43 cases (19.62%); the percentage of positive cases was 31.44% in women holding permanent jobs, 23.51% in cleaners, and 14.58% in unemployed housewives. It was concluded by the authors that chromates contained in a variety of household products used in routine cleaning operations are the cause of allergic sensitivity to chromates in women. No control or reference data were available.

Jovovic et al. (1977) have confirmed the allergic contact sensitivity of shoemakers exposed to chromates in occupational settings. Sixty percent of the shoemakers with allergic sensitivity showed a positive reaction to potassium dichromate. Allergic reactions in various glues to which the shoemakers were exposed were also reported.

Exposure to chromium may sensitize certain individuals resulting in asthmatic attacks upon subsequent re-exposure (NAS, 1974) (see Section 7.2.5.1).

7.1.3.2. SENSITIVITY TO CHROMIUM IN PROSTHESES -- In recent years, there has been an increase in the use of metal-to-plastic prostheses in orthopedic surgery. Many of the metal implants consist of alloys containing nickel, chromium, cobalt, and molybdenum.

Work by Swanson et al. (1973) and Coleman et al. (1973) has shown that when two cobalt/chrome alloy surfaces rub together, cobalt and chrome are released locally, pass into the blood and circulate throughout the tissue of the body, and are finally excreted in the urine. In patients sensitive to metal, the vessels supplying the bone in which the prosthesis is inserted may show obliterative changes, and in theory, lead to death of the bone, with weakening of the fixation between the bone and prostheses, and consequent loosening (Anonymous, 1976).

There is considerable conflicting evidence in this area, as Deutman et al. (1977) reported metal sensitivity in 4 of 66 patients induced by metal alloy implants following total hip replacement arthroplasty; however, positive patch tests occurred only with cobalt and nickel, while tests with chromium were negative. Brown et al. (1977) gave patch tests for chromium sensitivity to 20 patients with sterile loose hip replacements. Of these 20 patients, none were positive for chromium sensitivity, and of 17 patients that were reoperated on, none showed histologic evidence of delayed hypersensitivity around the implant.

In addition, contact dermatitis and allergic sensitivity to chromium-containing dental prostheses have been reported by Levantine (1974) and Ovrutskii (1976).

7.1.3.3. ANIMAL STUDIES ON CHROMIUM SENSITIVITY -- Numerous investigators have demonstrated that sensitization of laboratory animals can be produced by exposure to various chromium compounds, including both Cr(VI) and (III).

In studies of delayed dermal hypersensitivity to potassium chromate or chromium chloride, guinea pigs treated with 2.4×10^{-4} M chromic sulfate developed signifiant cross sections (Gross et al., 1968). The ability of Cr(III) compounds to evoke an allergic reaction in chromium-sensitive guinea pigs decreased gradually in the following order: chromic chloride > chromic nitrate > chromic sulfate > chromic acetate > chromic oxalate (Scheiner and Katz, 1973). According to the authors, this difference depended on the free Cr(III) concentration in the solution which, in turn, depended on the degree to which the Cr(III) formed coordination complexes with the original ligands present; strong ligands prevented the formation of complete antigens. Sensitization of guinea pigs with chromium (III) sulfate (using Triton X-100) was 86% successful, whereas sensitization with an aqueous solution of potassium chromate was successful in only 56% of the animals tested (Schwartz-Speck and Grundsmann, 1972).

Jansen and Berrens (1968) reported that guinea pigs could be sensitized to both Cr(III) and Cr(VI) by the subcutaneous injection of aqueous solutions of the appropriate chromium salts in a 1:1 emulsion with Freund's complete adjuvant.

Hicks et al. (1979) produced hypersensitization in guinea pigs with both Cr(VI) and (III) salts. The contact sensitization potentials of the Cr(III) complexes in guinea pigs were proportional to the release of chromium from the complex (Schneeberger and Forck, 1974). Siegenthaler et al. (1983) found that guinea pigs sensitized with either trivalent chromium chloride or potassium dichromate reacted *in vitro* and *in vivo* to challenges with both salts. They concluded that chromium-reactive lymphocytes are directed against common or closely related determinants.

7.2. EVALUATION OF THE CARCINOGENICITY OF CHROMIUM

The purpose of this section is to provide an evaluation of the likelihood that chromium is a human carcinogen and, on the assumption that it is a human carcinogen, to provide a basis for estimating its public health impact, including a potency evaluation in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic evidence. However, other factors, including mutagenicity, metabolism (particularly in relation to interaction with DNA), and pharmacokinetic behavior, have an important bearing on both the qualitative and the quantitative assessment of carcinogenicity. The available information on these subjects is reviewed in other sections of this document. This section presents an evaluation of the animal bioassays, the human epidemiologic evidence, the quantitative aspects of assessment, and finally, a summary and conclusions dealing with all of the relevant aspects of the carcinogenicity of chromium.

7.2.1. Animal Studies.

A number of animal studies have been performed to determine whether or not chromium compounds are carcinogenic. In these studies metallic chromium and salts of both the hexavalent (Cr VI) and trivalent (Cr III) states were administered by various routes. The discussions that follow are grouped according to these various routes of administration.

7.2.1.1. INHALATION STUDIES -- Baetjer et al. (1959) exposed three strains of mice (strain A, Swiss, and C57BL) to chromium-containing dust. These strains have, respectively, high, medium, and low spontaneous lung tumor incidences. The dust was similar to that found in the chromium chemical manufacturing industry, containing 13.7% hexavalent chromium oxide (CrO_3) and 6.9% trivalent chromium oxide (Cr_2O_3), along with other metal oxides. In addition to the chromium compounds in the dust, potassium dichromate ($K_2Cr_2O_7$) was added at a level of 1.0%. The animals were exposed to the dust-laden atmosphere containing between 0.5 and 1 mg of total chromium 4 hours/day, 5 days/week, for an average of 39.7 weeks (range of 16 to 58 weeks). Table 7-1 describes the specifics for each exposure group. At death or termination of exposure, the lungs were examined by means of a low-power microscope, and abnormal tissues were submitted for histologic confirmation of tumors.

TABLE 7-1. INHALATION EXPOSURE OF MICE TO CHROMIUM-CONTAINING DUST (Baetjer et al. 1959)

Strain	Sex	Number of animals at start	Number of animals at end	Duration of exposure (weeks)	Estimate of total Cr inhaled (mg of Cr)
Swiss	F	11	7	39	520
Swiss	M	10	6	39	520
Swiss	F	127	51	58	692
Strain A	F	34	31	16	141
Strain A	F	45	45	24	210
Strain A	F	110	38	38	359
Strain A	M	52	36	46	406
C57BL	M	50	13	42	667
C57BL	F	61	14	41	589

The incidence of lung tumors was not different in exposed mice of any strain as compared with approximately equal numbers of the appropriate strains of unexposed mice of the same age. There was also no difference in those strains having high spontaneous tumor incidence with regard to the average number of tumors per mouse or the percent of mice with multiple tumors. The lung tumors present in both control and treated animals were adenomas, which appeared to be histologically similar; however, in exposed animals, the adenomas developed slightly earlier in the strain A mice. Three additional small groups of mice (two groups of 10 Swiss female mice and one group of nine female strain A mice) were exposed to high concentrations of chromium dust (7.8 to 13 mg Cr/m^3) in a nose-only chamber 0.5 hours/day, 5 days/week, for 43, 52, and 20 weeks, respectively. Again, no increase in the incidence of lung tumors was observed.

In a lifetime chronic study, Nettesheim et al. (1971) exposed 136 C57BL/6 mice of each sex 5 hours/day, 5 days/week, to an atmosphere containing calcium chromate ($CaCrO_4$) dust at a level of 13 mg/m^3, with 95% of the particles less than 0.6 microns in size. During the study, seven or eight mice were removed for interim sacrifice at 6, 12, and 18 months; the sex distribution and exact number of animals removed at each period were not stated. At autopsy, sections were taken from all major organs, and with the exception of the lungs, it was indicated that no increase in tumor incidence was observed. In the lungs, tumors developed in six males and eight females, as compared with three males and two females in the control group. The tumors were described as alveologenic adenomas and adenocarcinomas, although the numbers of the different types of tumors were not given. The authors claim in the discussion that calcium chromate exposure resulted in a significant increase in lung tumors; however, the performance of statistical analysis was not described in the results. In a review of this study, the International Agency for Research on Cancer (IARC 1980) maintained that no excess in treatment-related tumors was observed. Because of difficulties in determining the numbers and sexes of the animals removed during the interim kills, it is impossible to perform independent statistical analysis of these data.

Two other experimental groups in the aforementioned study were exposed to calcium chromate dust following prior treatment with 100 R whole-body X-radiation or infection by influenza virus. A slightly greater incidence of lung tumors was observed after combined exposure to influenza virus, as compared with exposure to calcium chromate alone. As a result of exposure to two potential cancer-producing agents, these last two groups of animals cannot be used to provide any supporting evidence for the carcinogenicity of calcium chromate. With the limited experimental detail presented in this study, it is not possible to determine if the small increase in lung tumors represents a significant treatment-related increase in tumor incidence.

In the study described previously, Baetjer et al. (1959) also exposed 110 (57 males and 53 females) mixed-strain rats (from Wistar and McCollum stock) to the same chromium dust to which the mice were exposed; 100 rats (48 males and 52 females) of similar age distribution were kept as controls. The level of chromium in the air was 1 to 1.5 mg/m^3, with exposure again for 4 hours/day, 5 days/week, for >70 weeks. During the study, nearly half of the experimental rats died, three developed lymphosarcomas involving the lungs, while two additional suspected lymphosarcomas involving the lungs were also identified. No rats developed bronchogenic carcinomas. The authors considered these findings suggestive of a chromium-induced tumorigenic response; however, since lymphosarcomas are common in these rats, the experiment was repeated. In the second study (Steffee and Baetjer 1965), Wistar rats were exposed to chromium-containing dust under the same regime as described previously. Following autopsy, three alveogenic adenomas were detected in the treated rats and two in the controls, and four lymphosarcomas were present in both groups. From this second study, it was concluded that lymphosarcomas in rats are not associated with exposure to chromium-containing dust.

Also, Steffee and Baetjer (1965) exposed eight rabbits and 50 guinea pigs to mixed chromium dust containing 1.5 to 2.0 mg of total chromium/m^3 for 4 to 5 hours/day, 4 days/week, for 50 months and for life, respectively. The mixed chromium dust exposure consisted of 2 days/week exposure to roast dust, as described by Baetjer et al. (1959), supplemented with 1.0% dry potassium dichromate and the mist of a 5.0% solution of potassium dichromate, followed by a 1 day/week exposure to the mist of a 17.5% solution of sodium chromate and a 1 day/week exposure to residue dust (roast dust from which sodium chromate was extracted) supplemented with 1.0% dry potassium dichromate. There were no lung tumors in the rabbits, and the incidence of lung tumors and other body tumors was similar in the exposed and control guinea pigs. Under these experimental conditions, inhalation of mixed chromium dust did not increase the incidence of lung tumors.

Laskin (1972) conducted a study in which rats (number and strain not specified) were exposed by inhalation to air containing 2 mg/m^3 hexavalent calcium chromate. The total number of exposures was 589 over a period of 891 days. The author reported one squamous cell carcinoma of the lung and larnyx and one malignant peritoneal tumor. Because of incomplete reporting of the experiment, this study is considered to be inadequate to assess the carcinogenicity of calcium chromate by inhalation.

7.2.1.2. INTRATRACHEAL INSTILLATION STUDIES -- In further attempts to illustrate a lung tumorigenic response from chromium compounds, mixed chromium dust and chromium salts were instilled into the tracheas of experimental animals. Baetjer et al. (1959) suspended a chromium dust, similar in composition to that used in the inhalation studies, in olive oil, and zinc chromate and barium chromate in saline prior to intratracheal instillation into strain A, Swiss, and C57BL mice and mixed-breed rats (Wistar and McCollum stocks). The mice each received five to six instillations of 0.01 to 0.05 mg of chromium at 4- to

6-week intervals, while the rats received 15 instillations at the same dose at 2-week intervals. The total duration of the studies was between 32 and 52 weeks. The mice treated with chromium had a tumor incidence similar to age-matched controls, and the rats in both the treated and control groups had no benign or malignant tumors. In continuing work, Steffee and Baetjer (1965) treated 62 strain A mice with 0.01 to 0.03 mg chromium by intratracheal instillation of zinc chromate ($ZnCrO_4$). The instillations were performed at 2-week intervals for a total of six injections, and the animals were observed until death. The incidence of lung adenomas was 31 of 62 in the treated animals and 7 of 18 in the untreated controls. In the controls treated with zinc chromate, 3 of 12 animals developed lung adenomas. The incidence of lung tumors in treated animals was statistically different from controls. In the same study, the instillation of chromium dust, zinc chromate, and lead chromate ($PbCrO_4$) into the tracheas of guinea pigs (13 to 21 animals/group) and rabbits (7 to 10 animals/group) produced no increase in lung adenomas. Hueper and Payne (1962) also reported similar negative results after instillation of strontium chromate ($SrCrO_4$) or calcium chromate suspended in gelatin; however, the experimental detail in the report was insufficient for adequate evaluation. There is no convincing evidence that intratracheal instillation of chromium compounds results in the development of lung cancer.

Steinhoff et al. (1983 unpublished draft report) investigated the carcinogenicity of soluble sodium dichromate and calcium chromate in rats via intratrachael administration. The study consisted of 10 treatment groups, one negative control group, and two positive control groups. Each test group contained 40 male and 40 female Sprague-Dawley rats (10 weeks old at the beginning of the test). The design of the dose levels selected were such as to assess the impacts of the chemicals delivered in single high doses as contrasted to the same dose distributed over a 5-day period. Table 7-2 describes the dose levels used in this study.

TABLE 7-2. DOSAGE REGIMEN FOR INTRATRACHEAL INSTILLATION OF SODIUM DICHROMATE AND CALCIUM CHROMATE

(adapted from Steinhoff et al. 1983)

Test group[a]	Intratracheal instillation	
	1 time per week	5 times per week
Untreated	--	--
Physiological NaCl	5 mL/kg	1 mL/kg
$Na_2Cr_2O7 \cdot 2H_2O$	0.05 mg/kg	0.01 mg/kg
$Na_2Cr_2O7 \cdot 2H_2O$	0.25 mg/kg	0.05 mg/kg
$Na_2Cr_2O7 \cdot 2H_2O$	1.25 mg/kg	0.25 mg/kg
$CaCrO_4$	1.25 mg/kg	0.25 mg/kg

[a] Each group consisted of 40 male and 40 female Sprague-Dawley rats.

The study was conducted for 2 years and 8 months. The total dose administered for the highest dose group was 160 mg/kg. The dose levels of 5 x 0.25 mg/kg/week of sodium dichromate as well as calcium chromate were considered to be maximum tolerated doses. The maximum tolerated dose was demonstrated by the decline in the body weight gain and the increases in the absolute and relative lung weights; however, the decline in body weights was more pronounced in males than in females.

Rats administered sodium dichromate or calcium chromate one or five times per week had no significant reduction in survival periods as compared to controls, except in the case of females treated with calcium chromate 5 x 0.25 mg/kg week ($P \leq 0.05$ for saline controls and $P \leq 0.01$ for untreated controls).

The distribution of lung tumors (adenomas, adenocarcinomas, and squamous cell carcinomas) is presented in Table 7-3. An increased incidence of lung tumors as compared to controls was observed in only one treated group in which sodium dichromate was administered at 1 x 1.25 mg/kg/week. No lung tumors were observed in any of the groups treated with 5 x 0.01, 5 x 0.05, or 5 x 0.25 mg/kg/week,

TABLE 7-3. LUNG TUMOR INCIDENCE IN SPRAGUE-DAWLEY RATS FOLLOWING INTRATRACHEAL INSTILLATION OF SODIUM DICHROMATE OR CALCIUM CHROMATE
(Steinhoff et al. 1983)

Treatment group	Lung tumor incidence					
	Adenomas		Adeno-carcinomas		Squamous cell carcinomas	
	M	F	M	F	M	F
Untreated	0/40	0/40	0/40	0/40	0/40	0/40
Physiological NaCl 5x/wk	0/40	0/40	0/40	0/40	0/40	0/40
Physiological NaCl 1x/wk	0/40	0/40	0/40	0/40	0/40	0/40
$Na_2Cr_2O7 \cdot 2H_2O$ 5x0.01 mg/kg/wk	0/40	0/40	0/40	0/40	0/40	0/40
$Na_2Cr_2O7 \cdot 2H_2O$ 5x0.05 mg/kg/wk	0/40	0/40	0/40	0/40	0/40	0/40
$Na_2Cr_2O7 \cdot 2H_2O$ 5x0.25 mg/kg/wk	0/40	0/40	0/40	0/40	0/40	0/40
$Na_2Cr_2O_7 \cdot 2H_2O$ 1x0.05 mg/kg/wk	0/40	0/40	0/40	0/40	0/40	0/40
$Na_2Cr_2O_7 \cdot 2H_2O$ 1x0.25 mg/kg/wk	1/40	0/40	0/40	0/40	0/40	0/40
$Na_2Cr_2O_7 \cdot 2H_2O$ 1x1.25 mg/kg/wk	6/40[a]	6/40	2/40	0/40	3/40	3/40[a]
$CaCrO_4$ 1x1.25 mg/kg/wk	9/40	2/40	1/40	0/40	1/40[b]	1/40
$CaCrO_4$ 5x0.25 mg/kg/wk	5/40	0/40	0/40	0/40	0/40	1/40

[a] Included two tumors of doubtful origin. These were, in the first case (female rat), a squamous cell carcinoma, and in the second case (male rat), an adenocarcinoma in the paratracheal lymph nodes, probably metastases of tumors of unknown origin.

[b] Included a squamous cell carcinoma of the lung (male rat). It is not certain whether this was a primary lung tumor or a metastasis of a histologically proven squamous cell carcinoma of the jaw.

with the exception of one adenoma in a male rat treated with sodium dichromate (1 x 1.25 mg/kg/week). In rats administered calcium chromate, statistically significant increases in lung tumors were found in groups treated with 1 x 1.25 mg/kg/week, as well as in a group treated with 5 x 0.25 mg/kg/week distributed over a period of 5 days. Table 7-4 gives a retabulation of the results presented in Table 7-3, in which adenomas and adenocarcinomas were combined. The combined lung tumor incidence was statistically significant in male and female rats treated with 1 x 1.25 mg/kg/week of sodium dichromate. For calcium chromate, the combined adenomas and carcinomas were statistically significant only in male

TABLE 7-4. COMBINED LUNG TUMOR INCIDENCE IN SPRAGUE-DAWLEY RATS FOLLOWING INTRATRACHAEL INSTILLATION OF SODIUM DICHROMATE AND CALCIUM DICHROMATE (Steinhoff et al. 1983)

Treatment group	Lung tumor incidence			
	Adenomas and Adenocarcinomas		Squamous cell carcinomas	
	Male	Female	Male	Female
Untreated	0/40	0/40	0/40	0/40
Physiological NaCl 5x/wk	0/40	0/40	0/40	0/40
Physiological NaCl 1x/wk	0/40	0/40	0/40	0/40
$Na_2Cr_2O_7 \cdot 2H_2O$ 1x0.25 mg/kg/wk	1/40	0/40	0/40	0/40
$Na_2Cr_2O_7 \cdot 2H_2O$ 1x1.25 mg/kg/wk	8/40[a] P=0.003[b]	6/40 P=0.013[b]	3/40	3/40
$CaCrO_4$ 1x1.25 mg/kg/wk	10/40 P=0.0005[b]	2/40	1/40[c]	1/40
$CaCrO_4$ 5x0.25 mg/kg/wk	5/40 P=0.027[b]	0/40	0/40	1/40

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[a] Included two tumors of doubtful origin. These were, in the first case (female rat), a squamous cell carcinoma, and in the second case (male rat), an adenocarcinoma in the paratracheal lymph nodes, probably metastases of tumors of unknown origin.

[b] P-values calculated using the Fisher Exact Test.

[c] Included squamous cell carcinoma of the lung (male rat). It is uncertain whether this was a primary lung tumor.

rats treated with single weekly doses of 1.25 mg/kg/week, as well as with the same dose distributed over a period of 5 days (5 x 0.25 mg/kg). The adequacy of this study is validated by the carcinogenic effect of the positive controls dimethylcarbamylchloride and benzo[a]pyrene.

In conclusion, sodium dichromate and calcium chromate administered intratracheally in solution form in Sprague-Dawley rats resulted in positive carcinogenic effects.

7.2.1.3. INTRABRONCHIAL IMPLANTATION STUDIES -- Laskin et al. (1970) investigated the carcinogenic effects of chromium compounds using the intrabronchial pellet technique. The compounds used in this investigation were: chromic chromate, chromic oxide, chromic trioxide, calcium chromate, and process residue. Pellets were prepared from molten mixtures of materials dispersed in equal quantities of cholesterol carrier. These studies included material of differing solubilities and valences. A total of 500 rats were under observation for periods of up to 136 weeks. Lung cancers that closely duplicate human pathology were found in these studies (Table 7-5).

TABLE 7-5. CARCINOMAS PRODUCED WITH CHROMIUM COMPOUNDS IN RATS
(Laskin et al. 1970)

Material	Number of animals	Squamous cell carcinoma	Adeno-carcinoma	Heptocellular carcinoma
Process residue	100	1	-	1
Calcium chromate	100	6	2	1
Chromic chromate	100	-	-	1
Chromic oxide	98	-	-	-
Chromic trioxide	100	-	-	2
Cholesterol control	24	-	-	-

With the calcium chromate, eight cancers were found in an exposed group of 100 animals. Six of these were squamous cell carcinomas and the other two were adenocarcinomas.

The National Institute for Occupational Safety and Health (NIOSH 1975) criteria document on hexavalent chromium (Cr VI) described a written communication from L.S. Levy in 1975 about an animal study done at the Chester Beatty Research Institute, London. Random-bred Parton Wistar rats of both sexes received a pellet in the left inferior bronchiolus via trachectomy under anesthesia. The rats were kept for 2 years. One hundred rats were set up for each of the chromium-containing-material test groups. The pellets that were implanted contained 2 mg of test material suspended 50/50 (w/w) in cholesterol. Negative control groups received either blank metal pellets or pellets and vehicle. Positive control groups received 3-methylcholanthrene. The lungs of all rats either dying during the study or killed at its termination were examined both macroscopically and microscopically. Apart from those in the lung, tumors were similar both in type and number in all groups. The bronchial tumors found and microscopically confirmed are given in Table 7-6, along with the average induction periods. Additional lung tumors not of bronchial origin and not considered by the authors to be causally related to implantations are also listed in Table 7-6. The majority of bronchial tumors were large keratinizing squamous cell carcinomas. Intrathoracic invasions, particularly to the right lung in the hilar region, were common, and metastases to local lymph nodes and to kidneys were seen.

Squamous cell carcinomas were found in 8/100 ($P < 0.05$) rats receiving calcium chromate, 3/100 rats receiving zinc chromate (zinc potassium chromate), 3/100 rats receiving chromic chromate dispersed in silica, and 1/100 rats receiving ground chromic acid. It may be that the chromic acid implantation produced a carcinoma only because it was converted to a less-soluble hexavalent chromium material by reaction with cholesterol. Because of its extremely great oxidizing ability, some of the chromic acid may have been chemically reduced by cholesterol, forming chromic chromate. Calcium chromate produced carcinomas in 5/100 ($P < 0.05$) rats when mixed with primene, and carcinomas in 7/100 ($P < 0.05$) rats when mixed with diphenylguanidine. Primene 81-R benzoate and

TABLE 7-6. LIVING TUMORS FOUND AND MICROSCOPICALLY CONFIRMED
[Levy and Venitt (1975), NIOSH (1975)]

Experimental group no.	Compound no.	Test material	No. of rats in group	Bronchial carcinoma of left lung	Induction period in days (range)	Lung tumors not associated with treatment
1	1	Ground chromite ore	100	0	--	
2	2	Bolton high lime residue	"	"	--	
3	3	Residue after alumina precipitation	"	"	--	
4	4	Residue from slurry tank-free of soluble Cr	"	"	--	
5	5	Residue from vanadium filter	"	"	--	Pulmonary adenoma of left lung
6	6	Residue from slurry disposal tank	101	"	--	Anaplastic carcinoma of upper left lung Adenoma of right lung
7	7	Sodium dichromate dihydrate	100	"	--	Fibrosarcoma of upper left lung
8	8	Sodium chromate	"	"		
9	9	Chromic acid (ground)	"	1	560	
10	10	Chromic oxide	"	0	--	
11	11	Calcium chromate	"	8	604(473-474)	$P < 0.05$[a]
12	12	Chromic chloride hexahydrate	"	0	--	Lymphoma of right lung

(continued on the following page)

[a] P-value is calculated using the Fisher Exact Test (one-tailed).

[b] Zinc potassium chromate.

TABLE 7-6. (continued)

Experimental group no.	Compound no.	Test material	No. of rats in group	Bronchial carcinoma of left lung	Induction period in days (range)	Lung tumors not associated with treatment
13	13	Zinc chromate type II[b]	"	3	708(657-734)	
14	14	Chrome tan	"	0	--	
21	15A	Diphenylguanidine (DPG)	"	"	--	
22	15B	DPG + calcium	"	7	656(502-732)	$P < 0.05$[a]
23	16A	Primene 81-R benzoate	100	0	--	
24	16B	Primene + calcium chromate	"	5	620(440-732)	$P < 0.05$[a]
25	17A	Chromic chromate	"	0	--	
26	17B	Chromic chromate dispersed in silica	"	3	698(666-730)	
15	15	Pellet + cholesterol	150	0	--	Adenoma of right lung
16	16	Blank pellet	"	"	--	Adenocarcinoma of right lung
28	28	Pellet + cholesterol + Kieselguhr	100	"	--	
20	20	100% 3-MCA	48	34	493(217-730)	
17	17	100% 3-MCA	"	36	498(270-701)	
18	18	50% 3-MCA	"	18	474(284-696)	
19	19	25% 3-MCA	"	13	517(297-698)	
27	27	50% 3-MCA	50	36	498(269-732)	

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[a] P-value is calculated using the Fisher Exact Test (one-tailed)

[b] Zinc potassium chromate.

diphenylguanidine failed to produce tumors when administered by themselves. No bronchial carcinomas were found in negative control groups or in rats receiving sodium dichromate dihydrate or sodium chromate.

Levy and Martin (1983) conducted an extensive investigation of 21 chromium-containing test materials in Wistar rats, using an intrabronchial implantation technique. In this procedure, a stainless steel wire mesh pallet with anchoring hooks was loaded with approximately 2 mg of test material suspended in 2 mg of cholesterol as an inert carrier, and was surgically implanted into the lower left bronchus of 8-week-old rats. The study comprised 21 test groups, one vehicle-control group, and another positive control group. Details of the study design are given in Table 7-7. Weight gain and survival rate between the test and control groups showed a compound related effect. The rats were allowed to live for 2 years, after which the study was terminated. As shown in Table 7-7, an examination of the lung tissues indicated that bronchial carcinomas were found to be statistically significant in comparison with controls only in the groups given strontium chromate, zinc chromate, and calcium chromate. The authors of this study concluded that the carcinogenicity of chromium compounds depends on the extent of their solubility. Only sparingly soluble chromium compounds were observed to be carcinogenic.

7.2.1.4. INTRAPLEURAL INJECTION STUDIES -- Production of pulmonary tumors by the intrapleural injection of chromium compounds has also been attempted. Hueper and Payne (Hueper 1955, Hueper 1958, Payne 1960a, Hueper 1961, Hueper and Payne 1962) described a series of studies in rats treated by intrapleural injection of a number of hexavalent or trivalent chromium compounds. Hueper (1955) injected powdered metallic chromium into the pleural cavity of rats, guinea pigs, and mice under the dose schedule described in Table 7-8. No significant increase in tumor incidence, either at the injection

TABLE 7-7. INCIDENCE OF LUNG TUMORS IN RATS FOLLOWING INTRABRONCHIAL IMPLANTATION OF VARIOUS CHROMIUM COMPOUNDS
(adapted from Levy and Martin 1983)

Group no.	Test material	No. of rats[a]	No. of lungs examined	No. of bronchial carcinomas	Probability	Significance	Valence of chromium
1	Lead chromate	100	98	1	0.2 - 0.15	NS[b]	6
2	Primrose chrome yellow	100	100	1	0.2 - 0.15	NS	6
3	Strontium chromate	100	99	43	<0.00005	S[c]	6
4	Barium chromate	101	101	0	-	-	6
5	Molybdate chromate orange	100	100	0	-	-	6
6	Zinc chromate (low sol.)	100	100	5	0.015-0.010	S	6
7	Zinc tetroxychromate	100	100	1	0.2 - 0.15	NS	6
8	Cholesterol (negative control)	100	100	0	-	-	
9	Light chrome yellow	100	100	0	-	-	6
10	LD chrome yellow	100	100	1	0.2 - 0.15	NS	6
11	Calcium chromate (positive control)	100	100	25	<0.00005	S	6
12	Chromic acid	100	100	2	0.08 - 0.07	NS	6
13	Medium chrome yellow	100	100	1	0.2 - 0.15	NS	6
14	Zinc chromate (Norge)	100	100	3	0.05-0.04	S	6
15	Sodium dichromate	100	99	1	0.15-0.10	NS	6

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[a] For groups 1-22, 52 females and 48 males were used. For group 23, 24 females and 24 males were used.
[b] NS = Not statistically significant.
[c] S = Statistically significant at the 5% level.

(continued on the following page)

TABLE 7-7. (continued)

Group no.	Test material	No. of rats	No. of lungs examined	No. of bronchial carcinomas	Probability	Significance	Valence of chromium
16	High lime residue	100	99	1	0.15 - 0.10	NS	6 + 3
17	Vanadium solids	100	100	1	0.2 - 0.15	NS	6
18	High silica chrome ore	101	99	0	-	-	3
19	Kiln frit (2% limestone)	100	100	2	0.08 - 0.07	NS	6 + 3
20	Recycled residue (2% limestone)	100	100	0	-	-	6 + 3
21	Silica encaps. medium chrome yellow	100	100	0	-	-	6
22	Strontium chromate	100	99	62	<0.00005	S	6
23	20-methyl-cholanthrene (positive control)	48	48	22	<0.00005	S	6

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[a] For groups 1-22, 52 females and 48 males were used. For group 23, 24 females and 24 males were used.

[b] NS = not statistically significant.

[c] S = statistically significant at the 5% level.

TABLE 7-8. EXPOSURE SCHEDULE FOR BIOASSAY OF CHROMIUM COMPOUNDS BY INTRAPLEURAL INJECTION (Hueper 1955)

Species	Strain	Number of animals	Compound	Compound (mg)	Number of injections	Reference
mice	C57BL	50	metallic chromium powder	0.001	6 injections at 2-week intervals	Hueper 1955
mice	Strain A	55	mixed chromium dust	1 or 2	4 injections at 4- to 6-week intervals	Baetjer et al. 1959
rats	Bethesda Black	25	chromite roast	25	single implant	Hueper 1958
rats	Bethesda Black	35	chromite roast minus Na_2CrO_4	25	single implant in 50 mg of fat	Payne 1960a
rats	Bethesda Black	42	chromium acetate	25	8 implantations over 13 months	Hueper and Payne 1962
rats	Bethesda Black	39	$K_2Cr_2O_7$	2	single implant	Hueper and Payne 1962
rats	Bethesda Black	14	$CaCrO_4$	12.5	single implant	Hueper and Payne 1962
rats	Osborne-Mendel	25	metallic chromium powder	16.8	6 injections at monthly intervals	Hueper 1955
rats	Osborne-Mendel	25	chromite ore	36.7	6 injections at monthly intervals	Hueper 1955
guinea pigs	NR	26	metallic chromium powder	67.2	6 injections at monthly intervals	Hueper 1955

NR = Not reported.

site or in other organs, was observed. Payne (1960a) implanted chromite roast, from which the soluble sodium chromate was extracted, into the pleural cavity of 35 rats. Each rat received 25 mg of this material plus 50 mg of sheep fat, which corresponded to 2 mg of total chromium, of which 0.4 was hexavalent chromium. None of the 35 control animals developed tumors, while three of the treated animals developed implantation site tumors. In an earlier study (Hueper 1958) using chromite roast not leached of sodium chromate, none of the 25 treated male Bethesda rats developed implantation site tumors during 24 months; however, the early deaths of nine of the treated animals appreciably decreased the number of animals at risk. Hueper and Payne (1962) noted that no implantation site tumors were observed in 42 rats during a 24-month period following eight implantations of 25 mg of trivalent chromium acetate in gelatin over a 13-month period. Using a single implant of 2 mg of potassium dichromate into the pleural cavity, 1 of 39 rats developed a tumor at the implantation site. In this study, only calcium chromate elicited a high tumor incidence following implantation. Of the 14 rats treated with 12.5 mg of calcium chromate, eight developed tumors at the site of implantation. These studies suggest that intrapleural implantation of some hexavalent chromium compounds might be carcinogenic, with calcium chromate producing the most dramatic response. Hueper (1961) also reported that many hexavalent chromium compounds produce tumors upon intrapleural implantation, while trivalent compounds were less effective; however, no experimental detail, including dose, was provided. A summary of the tumor incidences reported is presented in Table 7-9.

Baetjer et. al. (1959) also used intrapleural injection to assess the carcinogenicity of mixed chromium dust, containing both trivalent and hexavalent chromium, in 30 male and 25 female strain A mice. The mice received four doses of dust suspended in olive oil, with each dose containing 0.07 mg of chromium

(Table 7-9). No increase in tumor incidence or number of lung tumors per mouse was observed during the period extending 52 weeks after the first treatment.

TABLE 7-9. COMPOUNDS REPORTED TO HAVE BEEN TESTED FOR CARCINOGENICITY BY INTRAPLEURAL IMPLANTATION[a]
(Hueper 1961)

Compound	Valence	Number of rats with tumors[b]	Percent of tumor incidence
Calcium chromate	+6	20	57
Sintered calcium chromate	+6	17	49
Strontium chromate	+6	17	74
Lead chromate	+6	3	9
Barium chromate	+6	1	3
Sodium dichromate	+6	0[a]	0
Zinc yellow	+6	22	63
Chromic chromate	+6, +3	26	74
Chromite roast residue	+6, +3	5	14
Chromium acetate	+3	1	3
Sheep fat controls	NA[c]	0	0

[a] All animals died by the 13th to 15th month of the study.
[b] There were 35 rats per group at the start.
[c] NA = Not applicable.

Davis (1972) injected trivalent chromite [$FeO(CrAl)_2O_3$] into the pleural cavity of 25 BALB/c mice and observed only small granulomas in the lungs. The animals were treated with a single injection of 5 mg of finely ground ore (≤ 1 um) containing 1 mg of chromium. The mice were killed at intervals of 2 weeks to 18 months, and the lungs were examined with the aid of an electron microscope.

A carcinogenic response was not observed in mice following intrapleural injection; however, the number of chromium compounds studied was limited.

The potential of trivalent chromium to produce lung tumors has been studied in the sensitive strain A mouse. Shimkin and Leiter (1940) injected 5 mg of chromite ore (39 to 60% Cr_2O_3) into the tail vein of 37 animals. Periodic kills of 10, 10, and 17 animals were performed at intervals of 2, 4, 5, and 6 months. respectively, and the lungs were examined for tumors. The mice treated with chromite ore had neither a greater incidence of lung tumors nor a greater number of tumors per tumor-bearing lung than the 72 control mice. More recently, Stoner et al. (1976) and Shimkin et al. (1978) reported similar negative results for trivalent chromium sulfate following intraperitoneal administration to strain A mice. In this study, groups of 20 mice received 100%, 50%, or 20% of the maximum tolerated dose (2,400 mg/kg) in 24 injections given three times/week. The animals were examined for tumors at the end of 30 weeks. In all of these studies, positive controls were used to demonstrate the sensitivity of the strain A mouse to the development of chemically induced multiple lung tumors.

Although increased risk of lung cancer has been associated with the chromium industry, as discussed below, it has proven difficult to demonstrate a carcinogenic response in the lungs of experimental animals. Trivalent chromium (Cr III) compounds have not produced lung tumors after inhalation, intratracheal implantation, or intrapleural implantation, while hexavalent chromium (Cr VI) was not carcinogenic by inhalation or intratracheal instillation. Some hexavalent chromium compounds did produce tumors following intrabronchial or intrapleural implantation; however, the small number of animals (14) used by Hueper and Payne (1962) in the study of calcium chromate, and the lack of detail in the report of Hueper (1961), where a number of hexavalent chromium compounds were reported to be carcinogenic, make it difficult to evaluate the carcinogenicity of these compounds to rodent respiratory tissue. For these reasons, studies of respiratory cancer in animals do not provide substantial confirmation of lung cancer associated with workers in the chromium industry. However, the limited data does suggest that of the two valences, hexavalent chromium is more likely to be the etiologic agent in chromium-induced cancer.

7.2.1.5. INJECTION STUDIES FOR SITES OTHER THAN LUNG -- Attempts have been made to demonstrate chromium-induced carcinogenesis in other than respiratory tissue. In an early study, Hueper (1955) injected either powdered chromium or chromite ore into the marrow cavity of the femur of rats, rabbits, and dogs. The experimental conditions are described in Table 7-10. Of the animals treated, only one rat developed a tumor at the site of injection, and other tumors observed in the treated and control groups were not considered to be treatment-related. Similar negative results were obtained by Hueper (1955) following intraperitoneal injection of chromium powder in rats and mice and intravenous administration of chromium powder in mice, rats, and rabbits. The experimental conditions used in these studies are also presented in Table 7-10. Although some tumors were present in treated rats, these tumors were similar to those in the controls, except in the cases of two treated rats that developed unique insulomas of the pancreas after intraperitoneal administration of powdered chromium, and two treated rats that developed lung adenomas. While no tumors were observed in the controls, the causal relationship between chromium exposure and the observed tumors is highly questionable.

Injection site tumors developed in animals after subcutaneous administration of chromium compounds in some, but not all, studies. Payne (1960a) treated groups of 52 C57BL mice (26 males and 26 females) with size-fractionated particles of chromium residue dust or chromic phosphate. The animals received a single subcutaneous injection of 10 mg, after which they were observed for life. The com-

TABLE 7-10. EXPERIMENTAL CONDITIONS USED TO STUDY THE EFFECT OF INTRAFEMORAL, INTRAPERITONEAL, AND INTRAVENOUS ADMINISTRATION OF CHROMIUM
(Hueper 1955)

Route	Species	Strain	Number of animals (M, F)	Chromium compound	Dose	Duration of observation
intrafemoral	rats	Osborne-Mendel	25 M	powdered chromium	100 mg	24 months
intrafemoral	rats	Wistar	25 M	powdered chromium	100 mg	24 months
intrafemoral	rabbits	Dutch	8 F	powdered chromium	140 mg	3 to 58 months
intrafemoral	dogs	mixed breed	5 F	powdered chromium	170 to 399 mg followed in 24 months by 340 to to 798 mg	60 months
intrafemoral	rats	Osborne-Mendel	15 M, 10 F	chromite ore 44% Cr_2O_3	36 mg	24 months
intrafemoral	rabbits	Dutch	4 F	chromite ore 44% Cr_2O_3	147 mg	20 to 50 months
intraperitoneal	mice	C57BL	50 M	powdered chromium	1 mg/week for 4 weeks	21 months
intraperitoneal	rats	Wistar	25 M	powdered chromium	5 mg/week for 6 weeks	NR
intravenous	mice	C57BL	25 M	powdered chromium	0.25 mg/week for 6 weeks	18 months
intravenous	rats	Wistar	25 M	powdered chromium	9 mg/week for 6 weeks	NR
intravenous	rabbits	NR	8 F	powdered chromium	2.5 mg/kg/week for 6 weeks, treatment repeated 4 months later	36 months

NR = not reported.

position of the dust fraction as related to trivalent and hexavalent chromium is presented in Table 7-11. A low incidence of injection site tumors (3 of 52) was observed in animals treated with the unfractionated residue dust, while no tumors were present in the controls or in animals treated with smaller particles, even though these smaller particles had a higher proportion of hexavalent chromium. In a study of identical design, Payne (1960b) treated mice with sintered chromium oxide, sintered calcium chromate, and calcium chromate. Only one injection site tumor was observed, and this was in an animal treated with calcium chromate. Roe and Carter (1969) reported that 20 weekly injections of calcium chromate at a dose of 5 mg for the first 2 weeks and 0.5 mg for the remaining 18 weeks, resulted in a 75% (18 of 24) incidence of injection site tumors. Although the title of Roe and Carter's (1969) article and the legend to the tabulated results described the route of administration as subcutaneous injection, the experimental section and the conclusions described the treatment as an intramuscular injection into the flank. As a result of this uncertainty, it is unclear whether any chromium compound has been demonstrated to produce injection site tumors following subcutaneous administration.

7.2.1.6. IMPLANTATION STUDIES -- Intramuscular implantation has also been used with varying success to demonstrate that chromium compounds are carcinogenic. Hueper (1958) and Payne (1960a) implanted chromite roast or chromium residue dust mixed with sheep fat into the thighs of Bethesda Black rats. The respective incidence of injection site tumors was 3 of 31 for animals given 25 mg of chromite roast and 1 of 35 for animals receiving the same doe of dust. In both studies, no tumors were present in the sheep fat-treated control animals. Payne (1960a) also implanted 10 mg of chromium dust into the thighs of 52 C57BL mice and observed no injection site tumors. Hueper and Payne (1959) and Payne (1960b) used similar techniques in the investigation of pure chromium compound.

TABLE 7-11. LEVELS OF HEXAVALENT CHROMIUM IN
FRACTIONATED RESIDUE DUST
(Payne 1960a)

Material	Weight of chromium as Cr/dose Hexavalent (mg)	Total (mg)
Vehicle (tricaprylin)	0	0
Dust residue extracted with H_2O	0.037	0.50
Dust residue 5 to 10	0.17	0.69
Dust residue <2	0.45	0.68
Chromic phosphate	0.003	2.64

In a small study, Payne (1960b) observed two injection site tumors in six Bethesda Black rats after implantation of a gelatin capsule containing 12.5 mg of calcium chromate. In the study by Hueper and Payne (1959), 25 mg of a chromium compound was mixed with sheep fat prior to implantation into groups of 35 Bethesda Black rats. The implantation site tumor incidence was 8 of 35 for calcium chromate, 8 of 35 for sintered calcium chromate, 15 of 35 for chromium oxide, and 0 for 35 for barium chromate. On implantation of 10 mg of sintered calcium chromate into the thighs of 52 C57BL mice; nine implantation site tumors developed; however, only one tumor developed following the implantation of calcium chromate. Hueper (1961) reported on the development of implantation site tumors following treatment of rats with a number of chromium compounds (Table 7-12); however, details of this study, including dose given, were not reported, and thus it is difficult to relate this study to the other reports of implantation

TABLE 7-12. COMPOUNDS REPORTED TO HAVE BEEN TESTED FOR CARCINOGENICITY BY INTRAMUSCULAR IMPLANTATION
(Hueper 1961)

Compound	Valence	Number of tumors[a]	Percent of tumor incidence
Calcium chromate	+6	9	25
Sintered calcium chromate	+6	12	34
Strontium chromate	+6	15	43
Lead chromate	+6	1	3
Barium chromate	+6	0	0
Sodium dichromate	+6	0	0
Zinc yellow	+6	16	46
Chromic chromate	+6, +3	24	69
Chromite roast residue	+6, +3	1	3
Chromium acetate	+3	1	3
Sheep fat control	NA	0	0

[a] There were 35 rats/group at the start.
NA = Not applicable.

site tumors. The intramuscular implantation technique has provided relatively consistent findings that some hexavalent chromium (Cr VI) compounds are tumorigenic in laboratory animals.

Neither trivalent (Cr III) nor metallic chromium compounds have produced implantation site tumors following intramuscular implantation. Hueper and Payne (1962) implanted 25 mg of chromic acetate into the thighs of 35 Bethesda Black rats. After a 24-month observation period, only one animal developed an injection site tumor. In a study using powdered chromium, Sunderman et al.

(1974) observed no tumors in 24 male Fischer rats after a 112-week observation period. Atomic absorption spectroscopy indicated that each rat received 2 mg of dust. Similar results were obtained by Hueper (1955) following repeated injection of powdered chromium into the thighs of 25 C57BL mice. Each animal received two injections of 0.1 mg at 2-week intervals, and this was repeated 3 weeks later for a total dose of 0.4 mg. No tumors developed in the 15 mice that survived 3 to 13 months. Although trivalent chromium was not tumorigenic following intramuscular implantation, only one compound was tested under a limited experimental protocol, and it is only speculative that zero-valent and trivalent chromium would continue to give negative results with further testing.

Maltoni (1974, 1976) gave single subcutaneous injections of 30 mg hexavalent lead chromate or hexavalent lead chromate oxide in water to groups of 40 Sprague-Dawley rats. Lead chromate produced 24/40 and 27/40 sarcomas respectively at the site of injection within 117 to 150 weeks. No local sarcomas were observed in 60 vehicle-treated control rats, and in 80 untreated control rats receiving comparable subcutaneous injection of unspecified iron pigments, only one local sarcoma was observed.

Furst et al. (1976) studied the carcinogenicity of hexavalent lead chromate and calcium chromate in rats. Groups of 25 male and 25 female Fischer-344 rats were given monthly intramuscular injections of 8 mg hexavalent lead chromate suspended in trioctanoin for 9 months or 4 mg hexavalent calcium chromate suspended in trioctanoin for 12 months.

Calcium chromate produced three fibrosarcomas and two rhabdomyosarcomas at the injection site in 5/45 rats, whereas hexavalent lead chromate produced 14 fibrosarcomas and 17 rhabdomyosarcomas at the site of injection in 31/47 rats. In addition, 3/24 lead chromate treated male rats developed renal carcinomas. None of the above tumors were found in controls injected with the vehicle.

Furst et al. (1976) also investigated the carcinogenicity of hexavalent lead chromate in mice. A total of 25 female NIH Swiss mice were given four monthly intramuscular injections of 3 mg hexavalent lead chromate in trioctanoin. Two lymphomas were observed within 16 months and three lung adenocarcinomas within 24 months among 17 mice necropsied. Similar incidences were observed in vehicle-injected and untreated female NIH Swiss mice.

7.2.1.7. ORAL STUDIES -- Trivalent chromium (Cr III) has been tested for carcinogenicity by the oral route in mice and rats. Schroeder et al. (1964) exposed a group of 108 (equal numbers of male and female) Swiss mice to drinking water containing 5 ppm of chromium as chromium acetate. The lifetime exposure to this level of chromium had no effect on the longevity of females, and only a slight decrease was noted in the longevity of males. There was no increase in tumor incidence in the treated animals as compared with controls. In a similar study, Schroeder et al. (1965) exposed 46 male and 50 female Long Evans rats to drinking water containing 5 ppm of chromium as chromium acetate. Again, lifetime exposure to this level of chromium had only a slight effect on longevity, with no increase in tumors in treated as compared with control animals. It should be noted that only one dose level of chromium was used in this study, and from the lack of overt signs of toxicity, it may be concluded that higher dose levels could be tolerated. Higher dose levels would increase the likelihood of detecting a carcinogenic response from a weak carcinogen. Lane and Mass (1977) observed carcinogenic activities of chromium carbaryl as well as synergistic activities with benzo[a]pyrene in rats following tracheal grafting techniques.

Ivankovic and Preussman (1975) incorporated trivalent chromium oxide into the diets of 60 male and female BD rats. The trivalent chromium oxide was baked into bread at levels of 1, 2, or 5%, and fed to the rats 5 days/week for

2 years. The only effect of treatment was a dose-dependent decrease in liver and spleen weight. Both the longevity and tumor incidence in the treated animals were similar to that of control animals. Again, the lack of major toxic effects of treatment may indicate that this chromium compound could have been tested at higher levels in the diet. The authors commented that the negative observations may have resulted from the poor absorption of chromium from the gastrointestinal tract.

7.2.1.8. SUMMARY OF ANIMAL STUDIES -- A summary of the animal carcinogenicity studies of chromium is presented in Table 7-13. To date, chromium compounds have not induced significantly increased incidences of tumors in laboratory animals following exposure by the inhalation and ingestion routes. Neither trivalent (Cr III) nor hexavalent (Cr VI) chromium compounds have induced significantly increased incidences of lung tumors by inhalation. Similar results have been obtained following the ingestion of trivalent chromium compounds; however, studies have not been reported in detail. There is some positive evidence that chromium, particularly some hexavalent chromium compounds, is carcinogenic following subcutaneous injection or intrabronchial, intrapleural, intramuscular, or intratracheal implantation; however, implantation site tumors have only consistently been demonstrated using intramuscular implantation. Of all the chromium salts, calcium chromate is the only one that has been consistently found to be carcinogenic in rats by several routes. Calcium chromate, strontium chromate, zinc chromate, sodium dichromate, lead chromate, lead chromate oxide, and sintered chromium trioxide have produced local sarcomas or lung tumors in rats at the site of application. Although the studies available indicate that metallic chromium powder and trivalent chromium compounds are not carcinogenic, these compounds have been studied less extensively than hexavalent chromium compounds. The relevance of studies using intramuscular implantation to human

TABLE 7-13. CARCINOGENICITY OF CHROMIUM COMPOUNDS IN EXPERIMENTAL ANIMALS

Route of administration	Compound	Species/ strain	Dose as chromium	Duration of exposure	Findings	Reference
inhalation	chromium-containing dust	mice/Strain A	0.5 to 1 mg/m^3	4 h/d, 5 d/wk for 16 to 54 wk	No increase in the incidence of lung tumors or number of tumors/lung	Baetjer et al. 1959
inhalation	chromium-containing dust	mice/Swiss	0.5 to 1 mg/m^3	4 h/d, 5 d/wk for 39 to 58 wk	No increase in the incidence of lung tumors or number of tumors/lung	Baetjer et al. 1959
inhalation	chromium-containing dust	mice/C57BL	0.5 to 1 mg/m^3	4 h/d, 5 d/wk for 41 to 42 wk	No lung tumors observed	Baetjer et al. 1959
inhalation	$CaCrO_4$ dust	mice/C57BL	4.33 mg/m^3	5 h/d, 5 d/wk for life	6 of 136 males and 8 of 136 females developed lung tumors as compared with 3 of 136 females and 2 of 136 male controls; the significance is not clear	Nettesheim et al. 1971
inhalation	chromium-containing dust	rats/mixed breed Wistar and McCollum	1 to 1.5 mg/m^3	4 h/d, 5 d/wk for >70 wk	Increased incidence of lymphosarcomas involving the lungs, 3 of 100 in experimental and 0 of 85 in control group	Baetjer er al. 1959
inhalation	chromium-containing dust	rats/Wistar	1 to 1.5 mg/m^3	5 h/d, 5 d/wk for life	No change in lung tumor incidence	Steffee and Baetjer 1965
inhalation	chromium-containing mist and dust	rabbits guinear pigs	1.5 to 2 mg/m^3	4 to 5 h/d, 4 d/wk the life of guinea pig or 50 months for rabbits	No increase in the incidence of lung tumors	Steffee and Baetjer 1965

(continued on the following page)

TABLE 7-13. (continued)

Route of administration	Compound	Species/ strain	Dose as chromium	Duration of exposure	Findings	Reference
intratracheal	chromium dust or $BaCrO_4$ or $ZnCrO_4$	mice/Strain A Swiss, C57BL	0.01 to 0.5 mg/ injection	5 to 6 injections at 4 to 6 wk intervals	No increase in the incidence of lung tumors or the number of tumors/lung	Baetjer et al. 1969
intratracheal	$ZnCrO_4$	mice/Strain A	0.01 to 0.03 mg/ injection	6 injections at 2 wk intervals	No statistical increase in lung tumors, 31	Steffee and Baetjer 1965
intratracheal instillation	chromium dust	rats/mixed breed Wistar and McCollum	0.02 mg/injection	15 injections at 2 wk intervals	No lung tumors observed	Baetjer et al. 1959
intratracheal instillation	$ZnCrO_4$ or $PbCrO_4$	rabbit	2.3 to 2.8 mg/ injection	3 to 5 injections at 3 mo intervals	No lung tumors observed	Steffee and Baetjer 1965
intratracheal instillation	$ZnCrO_4$ or $PbCrO_4$	guinea pigs	0.7 to 0.86 mg/ injection	6 injections at 6 wk intervals	No increase in lung tumor incidence	Steffee and Baetjer 1965
intratracheal application	$Na_2Cr_2O_7$	rats/ Sprague-Dawley	1 x per week 0.05 mg/kg/wk 0.25 mg/kg/wk 1.25 mg/kg/wk	30 months	Significant increased incidence of lung tumors at the highest dose	Steinhoff et al. 1983
			5 x per week 0.01 mg/kg/wk 0.05 mg/kg/wk 0.25 mg/kg/wk	30 months	No lung tumors observed	Steinhoff et al. 1983
intratracheal application	$CaCrO_4$	rats/ Sprague-Dawley	1 x per week 1.25 mg/kg/wk	30 months	Significant increased incidence of lung tumors	Steinhoff et al. 1983
			5 x per week 0.25 mg/kg/wk	30 months	Increased incidence of lung tumors	Steinhoff et al. 1983
intrapleural injection	Cr powdered metal	mice/C57BL	0.001 mg/ injection	6 injections at 2 wk intervals	No significant increase in injection site tumors	Hueper 1955
intrapleural injection	mixed chromium dust	mice/Strain A	0.07 mg/ injection	4 injections at 4 to 6 wk intervals	No increase in lung tumor incidence or number of lung tumors/ mouse	Baetjer et al. 1959
intrapleural injection	$FeO(CrAl)_2O_3$	mice/Balb/c	1 mg	single injection	Only small granulomas observed	Davis 1972
intrapleural injection	chromite ore	rats/Osborne-Mendel	36.7 mg (of ore)	6 injections at 1 mo intervals	No significant increase in injection site tumors	Hueper 1955
intrapleural injection	Cr powdered metal	rats/Osborne-Mendel guinea pigs	16.8 mg 67.2 mg	6 injections at 1 mo intervals	No significant increase in injection site tumors	Hueper 1955

(continued on the following page)

TABLE 7-13. (continued)

Route of administration	Compound	Species/ strain	Dose as chromium	Duration of exposure	Findings	Reference
intrapleural implant	chromite roast minus $NaCrO_4$	rats/Bethesda Black	25 mg (of roast)	single implant in sheep fat	3 of 35 animals developed implant site tumors; none in controls	Payne 1960a
intrapleural implant	$K_2Cr_2O_7$	rats/Bethesda Black	0.35 mg	single implant in sheep fat	1 of 39 animals developed implant site tumors; none in controls	Hueper and Payne 1962
intrapleural implant	$CaCrO_4$	rats/Bethesda Black	4.2 mg	single implant in sheep fat	8 of 14 animals developed implant site tumors, none in controls	Hueper and Payne 1962
intrapleural implant	$Cr(C_2H_3O_2)_3$	rats/Bethesda Black	5.2 mg/implant	8 implants over 13 mo	No implantation site tumors in 24 animals	Hueper and Payne 1962
intrapleural implant	chromite roast	rats/Bethesda Black	25 mg (of roast)	single implant	No implant site tumors	Hueper 1958
intrabronchial	variety of chromium compounds	rats/Parton Wistar	2 mg	single implant	See Table 7-6	Levy and Venitt 1975 (as reported in NIOSH 1975)
intrabronchial	21 compounds	rats/Parton Wistar	2 mg	single implant	See Table 7-7	Levy and Martin 1983
intrafemoral	metallic chromium	rat/Osborne-Mendel rats/Wistar rabbits/Dutch	100 mg 100 mg 140 mg	single injection	No injection site tumors developed except for a single tumor in one rat	Hueper 1955
intrafemoral	chromite ore	rats/Osborne-Mendel rats/Dutch	15 mg 64 mg	single injection	No injection site tumors	Hueper 1955

(continued on the following page)

Table 7-13. (continued)

Route of administration	Compound	Species/ strain	Dose as chromium	Duration of exposure	Findings	Reference
intrafemoral	metallic chromium	dogs/mixed breed	170 to 399 mg followed by 340 to 798 mg	second treatment given 24 mo after first	No injection site tumors	Hueper 1955
intraperitoneal	$Cr_2(SO_4)_3$	mice/Strain A	1.3 to 6.6 mg/ injection	24 injections given 3/wk	No increase in lung tumor incidence or number of lung tumors/mouse	Stoner et al. 1976; Shimkin et al. 1978
intraperitoneal	metallic chromium	mice/C57BL	1 mg/injection	4 injections at 1 wk intervals	No tumors observed	Hueper 1955
intraperitoneal	metallic chromium	rats/Wistar	5 mg/injection	6 injections at 1 wk intervals	Pulmonary adenomas in 2 of 25 animals; none in controls	Hueper 1955
intravenous	chromite ore	mice/Strain A	1.95 to 3 mg	single injection	No increase in lung tumor incidence or number of lung tumors/ mouse	Shimkin and Leiter 1940
intravenous	metallic chromium	mice/C57BL rats/Wistar	0.25 mg/injections 9.0 mg/injections	6 injections at 1 wk intervals	No tumors in mice while tumors in rats were identical to controls	Hueper 1955
intravenous	metallic chromium	rabbits/NR	2.5 mg/kg	6 injections at 1 wk intervals repeated in 4 mo	No adverse effects after 36 months	Hueper 1955

(continued on the following page)

Table 7-13. (continued)

Route of administration	Compound	Species/ strain	Dose as chromium	Duration of exposure	Findings	Reference
subcutaneous	chromium residue dust chromium residue dust, 5 to 10 p chromium residue dust, <2 p chromic phosphate sintered CrO_3 sintered $CaCrO_3$ $CaCrO_4$	mice/C57BL	0.5 mg 0.69 mg 0.68 mg 2.64 mg 0.52 mg 0.37 mg 0.33 mg	single injection	3 of 52 animals receiving chromium residue dust and 1 of 52 receiving $CaCrO_4$ developed injection site tumors	Payne 1960a,b
subcutaneous	lead chromate (VI) oxide	rats/ Sprague-Dawley	30 mg	single injection	injection site sarcomas in 27/40 treated and 0/60 vehicle control animals	Maltoni 1974, 1976
intramuscular	lead chromate (VI) oxide	rats/ Fischer 344	8 mg	single injection	injection site sarcomas in 31/47 treated and 0/22 vehicle control animals; 3 renal carcinomas	Furst et al. 1976
intramuscular	sintered chromium (VI) trioxide	rats/ Bethesda Black	25 mg	single implant	implantation site sarcomas in 15/35 treated and 0/35 control animals	Hueper and Payne 1959
intramuscular	metallic chromium	mice/C57BL	0.1 mg	2 injections at 2 wk intervals repeated 3 wks later	No tumors in 25 animals	Hueper 1955
intramuscular	$CaCrO_4$ sintered $CaCrO_4$	mice/C57BL	3.3 mg 3.3 mg	single implant	9 of 52 mice treated with sintered $CaCrO_4$ had implantation site tumors, while 1 of 52 treated with $CaCrO_4$ developed tumors	Payne 1960b
intramuscular	chromium residue dust	mice/C57BL	10 mg (of dust)	single implant	No injection site tumors developed	Payne 1960a
intramuscular	metallic chromium	rats/Fischer	2 mg	single implant	No tumors in 24 animals	Sunderman et al. 1974
intramuscular	$Cr(C_2H_3O_2)_3$	rats/Bethesda Black	5.2 mg	single implant	1 implantation site tumor in 35 treated animals	Hueper and Payne 1962

risk following inhalation or oral exposure to chromium compounds is not clear; however, these animal studies may indicate that some hexavalent chromium compounds are likely to be the etiologic agent in human chromium-related cancer.

7.2.2. Epidemiologic Studies.

7.2.2.1. CHROMATE PRODUCTION WORKERS -- The early association of respiratory cancer with employment in chromium compound-related industries has been reviewed by Baetjer (1950a). The first case report appeared in 1890, with a total of 122 reports of respiratory cancer in chromium compound-related industries collected between this date and 1950. These cases were predominantly in German and American industries, with one case reported in Scotland and one case reported in Switzerland. The workers in the chromate industry were exposed to chromite ore (trivalent chromium) and sodium monochromate, sodium bichromate, and chromic acid (hexavalent chromium), along with vapors and gases associated with the chromate manufacturing process. According to Baetjer, the early German investigators suggested that hexavalent chromium was the etiologic agent in respiratory cancer, since respiratory cancer was not associated with the mining of trivalent chromite ore. These early observations do not provide information on the relative incidence of respiratory cancer in the chromate workers as compared with the general population, nor were the studies sufficiently large or controlled to support the conclusion that chromium exposure was related to respiratory cancer. However, these early reports were the impetus for initiating a number of epidemiologic studies of the chromate manufacturing industry in the United States, Great Britain, and Japan. Although a relatively large number of epidemiologic studies have been conducted of this industry, the individual studies were often analyzing cancer incidence from the same cohort of workers. In order to clarify the interrelationship of the cohorts in these studies, the locations of the plants from which each study derived its exposed population are presented in Table 7-14. It should be noted that studies of the same plant by different investigators often resulted in the vital statistics of individual workers being used in more than one study. The result was that in many cases, these epidemiologic studies verified the observations of previous studies rather than adding evidence from additionally exposed population groups.

In response to the early reports associating lung cancer with the chromate industry, the industry initiated a retrospective epidemiologic study of the seven chromate plants in the United States (Machle and Gregorius 1948). A total of 1,445 workers were employed in the seven plants, with each plant employing between 50 and 500 workers. The company group life insurance records were used to determine causes of death. Adequate records were available for six of the plants, and the cohort of men actively working in the chromate industry consisted of 11,019 man-years of experience. In this cohort, 156 deaths were observed, 32 of which were from lung cancer. An additional 10 lung cancer deaths were reported of the 37 deaths from the plant with work records unsatisfactory for the purpose of the epidemiologic analysis. The period of study varied with each plant from 4 to 17 years, depending on the availability of mortality data. Of the total deaths observed in the chromate industry, 21.8% (42 of 193) were from lung cancer, compared to an expected 1.3% (10 of 733) as calculated from a comparable industrial group not exposed to chromium (industrial life insurance policyholders for the year 1947, Metropolitan Life Insurance Co.). This difference is statistically significant at $P < 0.01$. When examined individually, five of the seven plants were reported to have respiratory cancer proportionate mortality ratios from 13 to 31 times that expected. The crude respiratory cancer mortality rate per 1,000 males was also found to be significantly ($P < 0.01$) increased over the crude lung cancer mortality rate of the group of life insurance holders. This was

TABLE 7-14. LOCATION OF CHROMATE MANUFACTURING PLANTS WHICH PARTICIPATED IN EPIDEMIOLOGIC STUDIES AND PLANTS FROM WHICH VITAL STATISTICS WERE OBTAINED FOR EACH STUDY

Location of plant	Machle and Gregorius 1948	Brinton et al. 1952 (also pub. as part of PHS 1953)	Mancuso and Hueper 1951	Mancuso 1975	Baetjer 1950a	Hayes et al. 1979	Hill and Ferguson 1979	Taylor 1966	Enterline 1974	Bidstrup 1951	Bidstrup and Case 1956	Alderson et al. 1981	Ohsaki et al. 1978	Watanabe and Fukuchi 1975	Satoh et al. 1981	Korallus et al. 1982	Bittersohl 1971
Glens Falls, NY	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Jersey City, NJ																	
Plant #1	+	+	-	-	-	-	-	+b	+b	-	-	-	-	-	-	-	-
Plant #2	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Baltimore, MD	+	+	-	-	+	+	+	+	+	-	-	-	-	-	-	-	-
Kearny, NJ	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Newark, NJ	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Paines-ville, OH	+	+	+	+	-	-	-	+	+	-	-	-	-	-	-	-	-
Bolton, England	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-
Rutherglen, England	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-
Eaglescliff, England	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-

+ = Participating chromate manufacturing plants.
- = Non-participating chromate manufacturing plants.

[a] The plant in the Watanabe and Fukuchi (1975) and the Ohsaki et al. (1978) studies may be one and the same; it is impossible to tell from the literature. Both plants were reported to be located on Hokkaido Island, Japan.

[b] Plant #1 is the larger of the two plants. Machle and Gregorius (1948) reported that it had 350 employees as compared to 150 employees in Plant #2.

TABLE 7-14. (continued)

Location of plant	Machle and Gregorius 1948	Brinton et al. 1952 (also pub. as part of PHS 1953)	Mancuso and Hueper 1951	Mancuso 1975	Baetjer 1950a	Hayes et al. 1979	Hill and Ferguson 1979	Taylor 1966	Enterline 1974	Bidstrup 1951	Bidstrup and Case 1956	Alderson et al. 1981	Ohsaki et al. 1978	Watanabe and Fukuchi 1975	Satoh et al. 1981	Korallus et al. 1982	Bittersohl 1971
Hokkaido Islands, Japan	-	-	-	-	-	-	-	-	-	-	-	-	+[a]	+[a]	-	-	-
Tokyo, Japan	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
Leverkusen, W. Germany	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Uerdingen, W. Germany	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Leuna Chemical Combine, E. Germany	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+

+ = Participating chromate manufacturing plants.
- = Non-participating chromate manufacturing plants.

[a] The plant in the Watanabe and Fukuchi (1975) and the Ohsaki et al. (1978) studies may be one and the same; it is impossible to tell from the literature. Both plants were reported to be located on Hokkaido Island, Japan.

[b] Plant #1 is the larger of the two plants. Machle and Gregorius (1948) reported that it had 350 employees as compared to 150 employees in Plant #2.

true for both the age group 50 and under and the age group 50 and over. A slightly increased crude mortality rate from digestive system cancer was also reported (1.18 per 1,000 versus 0.59 per 1,000, $P < 0.01$).

Estimates of exposure were not made in this study, since analytical data were not available for a large portion of the period studied, and work records did not report the shifting of personnel to different positions in the plant during the course of employment. A limitation of this study is that no age adjustment was done in the comparison of the mortality rates of the control group with the mortality rates of the exposed group. In this regard, however, it should be noted that there was a dramatic difference in lung cancer mortality between the chromate workers and the control group for both the 50 and under age category and the over 50 age category. Thus, it is unlikely that a preponderance of older persons among the chromate workers was responsible for the large difference in lung cancer mortality between the chromate workers and the control group. Another limitation is that the authors used a lung cancer mortality rate for oil refinery workers in the 1933-1938 period for comparison with the chromate workers in the 1930-1947 period. Lung cancer increased dramatically in U.S. males between 1930 and 1947 (about five times). Thus, it is possible that the lung cancer mortality rate for the control group may have a lower rate than that which would have been found for the period 1930-1947. However, it is unlikely that the dramatic difference in lung cancer between the controls and the chromate workers could be explained by the selection of a control group from a slightly different time period than that of the exposed group.

Brinton et al. (1952) used the disability records between January 1, 1946 and December 31, 1950 of the seven United States chromate plants to determine occupational diseases associated with the chromate industry. These data were subsequently published as part of the Public Health Service (1953) report, "Health of Workers in a Chromate-Producing Industry." The cohort was limited to men who belonged to the company disability plan, which prior to 1949 was voluntary. After 1949, participation in the plan was mandatory in all but two plants, although participation in these plants was near 100% by the end of the study. Only deaths that occurred within 1 year of beginning disability status were included in this study, and the determination of the cause of death was made solely on what was listed as "cause of death" on the death certificate. The health experience of a "large group of industrial workers (predominantly white)" was used for comparison. The incidence of most disabilities was comparable between chromate workers and the reference population, with the exception of cancer. Cancer at all sites had an incidence of 7.1 per 1,000 in chromate workers and 0.7 per 1,000 in the control population ($P < 0.01$); however, it should be pointed out that the actual number of individuals who developed cancer was small (26 individuals) in the group of chromate workers. Brinton et al. (1952) further studied the cancer experience in the chromate industry for the period 1940-1950, using death records obtained from the group disability insurance plans. Information was available for two plants for the entire 1940-1950 time period: one plant had records for 1943 to 1950, three plants for 1946 to 1950, and one plant for 1949 to 1950. During this 11-year period, 44 deaths from cancer at all sites and 32 deaths from respiratory cancer were observed. This corresponds to a 4.5-fold increase in cancer at all sites and a nearly 29-fold increase in respiratory cancer in the chromate workers as compared to males in the United States as a whole. There was an indication in the data that the increased risk of respiratory cancer was greater in nonwhite as compared to white chromate workers; however, the number of individuals was small when the cohort of chromate workers was subjected to this further subdivision. The authors commented on the limitations the study placed on the make-up of the cohort as a result of the use of death records obtained solely from the company disability plan, and suggested that the observed increased risk of respiratory cancer represents a minimal value.

Baetjer (1950a, b) studied a cohort consisting of lung cancer patients in two Baltimore hospitals to determine if employees of the local chromate plant were overrepresented in this group. The records from Johns Hopkins Hospital were examined for the period from 1925 to 1946, and from Baltimore City Hospital from 1930 to 1948; 198 and 92 confirmed cases of lung cancer in males were obtained, respectively, from each institution. Control groups consisted of age-matched male patients with a hospital stay of >10 days chosen at random from the hospital records. An additional control was used for Johns Hopkins; this consisted of patients with cholelithiasis, since patients with this disease, as well as lung cancer patients, may preferentially select a large medical facility. At Johns Hopkins, 7 of 198 lung cancer patients had worked in the chromate industry; none of the 226 randomly sampled controls and none of the 177 cholelithiasis controls had worked in the chromate industry. At the Baltimore City hospital, 4 of 92 lung cancer patients and 0 of 499 control patients reported exposure to chromium compounds. The percentage of chromate workers in the lung cancer group was statistically signficantly ($P < 0.01$) greater than expected. If one were to calculate the unadjusted odds ratios of having lung cancer and being exposed to chromium, the odds ratios would be about 32 for the Johns Hopkins cases and about 23 for the Baltimore City Hospital cases. Both are statistically significant ($P < 0.05$).

Mancuso and Hueper (1951) used vital statistics for all employees who worked for $\geq$ 1 year in the Painesille, Ohio chromate plant during 1931 to 1949 to investigate chromate production-associated lung cancer. Of the 2,931 deaths of males in the county where the plant was located, 34 (1.2%) were from respiratory cancer, while of the 33 deaths among the chromate workers, 6 (18.2%) were from respiratory cancer. This difference is significant at $P < 0.01$. Mancuso and Heuper (1951) indicated that 96% of the workers were exposed predominantly to insoluble chromate. Chemical analysis of the organs of two deceased workers, one who had died from lung cancer and one who had died from bladder cancer, revealed that the lungs appeared to be the major storage depot for chromium, with approximately 390 and 250 ug of chromium per 10 g of tissue detected in each individual respectively. The high level of chromium in the first subject, the one who had died from lung cancer, was still detected despite the fact that the individual had not been exposed to chromium for a period of 3.4 years. Chromium levels measured in the lungs of nonexposed individuals were nearly zero. Mancuso and Hueper (1951) suggested that the presence of insoluble chromium in the lung may have been an etiologic factor in the observed higher incidence of cancer; however, the present data are too limited to support this conclusion.

Mancuso (1975) followed the vital status until 1974 of 332 chromate plant workers from his earlier study (Mancuso and Hueper 1951) who had been employed from 1931 to 1937. Over 50% of the 332 employees in this cohort had died by 1974. Mancuso divided this group of workers into those employed from 1931 to 1932, 1933 to 1934, and 1935 to 1937. He found that 63.6%, 62.5%, and 58.3%, respectively, of the cancer deaths in these groups were lung cancer deaths. The latency period for the lung cancer deaths was found to cluster around 27-36 years. The author found that lung cancer deaths were dose-related to insoluble (trivalent), soluble (hexavalent), and total chromium exposure, and concluded that lung cancer mortality was associated with both trivalent and hexavalent chromium. Workers in this study were exposed to both trivalent and hexavalent chromium, and as exposure to one increased so did exposure to the other. Therefore, an observed dose-response to trivalent chromium may merely be a reflection of a dose-response to hexavalent chromium, or vice versa. Thus, it is questionable whether the author's conclusion with regard to a dose-response to both hexavalent and trivalent chromium is correct. Furthermore, the lung cancer death rates, which purport to show this dose-response, are based on very small numbers and thus the finding of dose-response is probably questionable. For six deaths due to lung cancer, chromium levels well above control values were found in the lungs of the deceased at autopsy 15-195 months after the last exposure to chromium, suggesting that the lung retains chromium for a considerable period of time.

Taylor (1966) studied a group of 1,212 chromate workers for 24 years using Old-Age and Survivors Disability Insurance records. All of these workers were employed in three United States chromate plants (Baltimore, Maryland; Painesville, Ohio; and the larger of two plants in Jersey City, New Jersey) for ≥ 3 months during the period 1937 to 1940. The vital statistics of the group were obtained through 1960, and where deaths occurred, the cause was determined from death certificates. Causes of death in this cohort were compared with age- and cause-specific mortality rates for civilian males in the United States. The most dramatic increase in the standardized mortality ratio (SMR) for chromate workers occurred in respiratory cancer, with excesses of 8.5 times (71 observed and 8.3 expected) observed by the termination of the study in 1960. Also, the length of experience in the chromate industry, used as the only indication of the extent of exposure, was compared with the incidence of lung cancer in this cohort. After 1937, duration of employment was determined from insurance records, while prior to this date, duration of employment was determined by extrapolation from the age-specific employment experience of the cohort. Using this method to determine length of exposure, Taylor found that respiratory cancer mortality showed a dose-response by length of time exposed to chromate.

Bittersohl (1971) studied cancer incidence among more than 30,000 employees of the Leuna Chemical Combine in the German Democratic Republic (East Germany). The chemical plant comprised several departments involving different chemical exposures. Ever since the plant had opened (in 1921 or earlier), its workers had experienced increasing cancer incidence. During the period 1958 to 1971, 588 malignancies were found among the male workers and 170 malignancies were found among the female workers. In most of the departments, no cases of cancer were found. However, in those departments with exposures to asbestos and tar, coal gases, ammonia, or isobutyl oil, or exclusive exposure to asbestos, chromate, or coal gases, the cancer incidence per 10,000 was much higher relatively than the average for the plant. In chromate production, the cancer rate was about ninefold higher than that of departments where the above-described exposures did not exist. This rate exceeded the rates in departments with exposure to either asbestos or coal gases. It was less than the cancer rate for departments where there was exposure to asbestos and tar, coal gases, ammonia, or isobutyl oil.

This study appears to be nothing more than an interdepartmental comparison of cancer incidence rates within a chemical works. The author has not defined a cohort for his study, and thus the results could be misleading with regard to the cancer experience of chromate production workers if there was a high turnover rate by department. In connection with the data that are presented, the author has provided little detail. Organ-specific cancer incidence is not given, and the author does not state whether he is comparing crude rates or rates that are sex- and age-adjusted. Thus, although the cancer incidence rate for the chromate production workers is strikingly high in comparison with nonexposed workers, the study design and lack of detail render the results somewhat inconclusive.

Enterline (1974) recalculated the expected deaths for the study by Taylor (1966), but provided no explanation as to why this was done. Enterline calculated a respiratory cancer SMR of 942 for the 20-year observation period from 1940 to 1960. Taylor had calculated a respiratory cancer SMR of 850 for the period from 1937 to 1960. Enterline (1974) showed that the relative risk of respiratory cancer was greater in workers in the age group <45 years (14.1 times) as compared with the older age group of 55 to 64 (6.8 times). Enterline also showed that the risk of respiratory cancer was highest shortly after the cohort was identified, suggesting "a short latent period which is probably the result of exposure to a very potent carcinogen."

Hayes et al. (1979) conducted a cohort mortality study of workers at a Baltimore, Maryland, chromium chemical production plant. The plant underwent extensive changes in the mill and roast operation and bichromate operations in 1950 and 1951, when a new facility was built to house these operations, and in the chromic acid and special products operations in 1960, when a new facility was built to house these operations. The new facilities were constructed for the purpose of lowering employee exposure to chromium. In this study, vital status was determined on newly hired workers between 1945 and 1974 who had at least 90 days of employment. The cohort consisted of 2,101 employees, 1,803 laborers, and 298 managers, of which vital statistics were obtained for 88% of the group as of 1977. A comparison of lung cancer in this cohort was made using SMRs from the cause-specific mortality rates of Baltimore males, and was tested for significance by means of the Poisson probability distribution. Workers were divided into two exposure groups; the high or questionable exposure group consisted of employees who worked in the old facilities and workers of unknown exposure, and the low exposure group consisted of workers employed only in the new facilities. In this study, no information was available on the actual levels of exposure or the extent of difference in exposure between the new and old plants. Analysis of lung cancer mortality by specific jobs was done after matching lung cancer cases by race, age, time of initial employment, and duration of employment to employees that died from noncancer causes.

The SMR for lung cancer in the entire cohort of hourly workers was 202 (95% confidence limits of 155 to 263), which was statistically significant ($P < 0.01$). The SMRs for both short-term (90 days to 2 years) and long-term ($\geq$ 3 years) workers of the high and low exposure groups are presented in Table 7-15. There was an apparent dose-response relationship, as associated with length of employment, for the group initially hired between 1950 and 1959. The lung cancer SMR was statistically signficant (95% confidence limits did not include 1.00) for the workers with "high and questionable exposure" employed >3 years, and who had initially been employed between 1950 and 1959. In analyzing lung cancer by job description, only workers in the special products department or employees who worked in both the special products and bichromate departments, the so called "wet end" of the production process (the production process in the mill and roast department is referred to as the "dry end"), showed a significantly ($P < 0.05$) elevated relative risk of lung cancer of 2.6 and 3.3, respectively.

In a study of the same plant investigated by Hayes et al. (1979), Hill and Ferguson (1979) used a novel statistical analysis in an attempt to demonstrate any trends in the risk of lung cancer associated with the modernization of the plant. The statistical method used was "probability window analysis," which provided a method of comparing the number of cases of lung cancer in equivalent time periods. In comparing the number of lung cancers prior to 1951 (the time

TABLE 7-15. OBSERVED NUMBER OF DEATHS, STANDARDIZED MORTALITY RATIOS (SMRs), AND 95% CONFIDENCE LIMITS (95% CL) FOR DEATHS DUE TO CANCER OF THE TRACHEA, BRONCHUS, AND LUNG AND THE NUMBER OF REPORTED DEATHS FOR WHICH NO CERTIFICATE COULD BE OBTAINED, BY YEAR OF INITIAL EMPLOYMENT, EXPOSURE CATEGORY, AND TOTAL DURATION EMPLOYED, FOR WORKERS INITIALLY HIRED AS HOURLY EMPLOYEES
(Hayes et al. 1979)

		Exposure category[a]			
		Low exposure		Questionable and high exposure	
Duration of employment[b]	Cause of death	Observed no. of deaths	SMR (95% CL)[c]	Observed no. of deaths	SMR (95% CL)[c]
		INITIALLY HIRED 1945 to 1949			
Short	Trachea, bronchus and lung	NA	NA	20	1.8 (1.1 to 2.7)
	Cause not determined[d]	NA	NA	25	NA
Long	Trachea, bronchus and lung	NA	NA	13	3.0 (1.6 to 5.2)
	Cause not determined[d]	NA	NA	0	NA

[a] Based upon whether work exposure was exclusively in a new facility. See text.

[b] Short: 90 days to 2 years; long: $\geq$ 3 years.

[c] Calculated using an assumption that the observed number of deaths is distributed as a Poisson random variable, $P = 0.025$, in each tail.

[d] Those reported deceased for whom no death certificate could be obtained. If these are distributed by cause of death in a similar way as the known deaths (cancer of the trachea, bronchus, and lung, 15%), the reported SMRs would be increased slightly.

NA = Not applicable.

(continued on the following page)

TABLE 7-15. (continued)

		Exposure category[a]			
		Low exposure		Questionable and high exposure	
Duration of employment[b]	Cause of death	Observed no. of deaths	SMR (95% CL)[c]	Observed no. of deaths	SMR (95% CL)[c]
		INITIALLY HIRED 1950 to 1959			
Short	Trachea, bronchus and lung	2	0.7 (0.1 to 2.6)	12	1.8 (0.9 to 3.1)
	Cause not determined[d]	3	NA	7	NA
Long	Trachea, bronchus and lung	3	4.0 (0.8 to 11.7)	9	3.4 (1.6 to 6.5)
	Cause not determined[d]	0	NA	0	NA
		INITIALLY HIRED 1960 to 1974			
All	Trachea, bronchus and, lung	0	NA	0	NA
	Cause not determined[d]	0	NA	0	NA

[a] Based upon whether work exposure was exclusively in a new facility. See text.

[b] Short: 90 days to 2 years; long: ≥ 3 years.

[c] Calculated using an assumption that the observed number of deaths is distributed as a Poisson random variable, P = 0.025, in each tail.

[d] Those reported deceased for whom no death certificate could be obtained. If these are distributed by cause of death in a similar way as the known deaths (cancer of the trachea, bronchus, and lung, 15%), the reported SMRs would be increased slightly.

NA = Not applicable.

of start-up of the new bichromate plant) with those after 1951, Hill and Ferguson (1979) report a statistically significant ($P < 0.01$) decline from 23 to 7, and the authors suggested that this reduced risk of lung cancer resulted from the engineering improvements that took place in 1951. Comparing the time periods 1932-41, 1942-51, 1952-61, and 1962-71, the number of bronchogenic carcinoma deaths falling within these time periods ("windows") are 9, 7, 1, and 0, respectively. The authors found a significant ($P < 0.01$) difference when comparing the four groups under the null hypothesis that all classes have equal probabilities of cancer mortality. The CAG would agree with the review of this study by the IARC (1980), in which it was stated that no conclusion on improved safety in this chromate plant could be made, since the analysis only compared lung cancer cases and not rates of lung cancer. Also, this analysis does not allow for the long latency period generally associated with lung cancer in the chromate industry.

Chromate plants in both England and Japan have also been studied to determine if there is an association between employment in this industry and lung cancer. In an early survey, Bidstrup (1951) performed lung X-rays of 724 workers employed in the three chromate plants in England in 1949. This survey detected only one case of lung cancer, while the expected number would have been 0.4, as indicated from the mass radiography units of the Ministry of Health. Of the 724 workers examined, 237 were employed for $\geq$15 years, and although the numbers were too small for definite conclusions, Bidstrup (1951) suggested that it was unlikely that a 25-fold incrased risk of lung cancer, as reported in studies of United States plants, was associated with employment in the British plants. Bidstrup's study was a cross-sectional study of only currently employed workers, however. Since workers with lung cancer or with symptoms of lung cancer are likely to have dropped out of the working population, it is probable that such results underestimate the difference in the incidence or the risk of lung cancer in this group of workers.

Bidstrup and Case (1956) performed a follow-up study between 1949 and 1955 of the 723 workers who participated in the radiographic survey. During this time, 217 workers were lost to the study as a result of change in employment. Of the remaining men, all but 59 were alive in 1955 when the study was terminated. The age- and cause-specific deaths of these chromate workers were compared with the number expected based on vital statistics for the male population of England and Wales. There was no difference in either death rates for neoplasms other than lung cancer or deaths from other causes; however, for lung cancer, there were 12 observed deaths with only 3.3 expected. This increase of 360% was statistically significant ($P = 0.005$). There was also a trend for greater risk in the age group <45 years (7 observed and 1.3 expected; $P < 0.01$, as calculated by the CAG); however, the numbers were too small to demonstrate if this trend was statistically significant. The effects of place of residence, social class, and smoking habits on lung cancer incidence were considered too small to account for this 360% increase in risk. The authors noted that this study was of short duration and that continued follow-up of this cohort would probably reveal an even greater increased risk of lung cancer. Of interest in this study is the authors' report that 217 workers were lost to follow-up because of change in employment. Change of employment may well indicate a change in health status, and thus may suggest that the difference in lung cancer mortality may again be underestimated.

Alderson et al. (1981) conducted a cohort mortality study of workers at three chromate plants in Great Britain. This was follow-up of the earlier studies by Bidstrup (1951) and Bidstrup and Case (1956). Subjects were eligible for this study if they had had an X-ray examination at work, had worked for a minimum of one year's continuous service, and had been employed from 1948 to 1977. Two of the plants, those at Bolton and Rutherglen, were closed in 1966 and 1967, respectively. Following these closings, production became concentrated at the Eaglescliffe plant. The national mortality rates for England and Wales were used to calculate expected mortality for the plants at Bolton and Rutherglen. For all plants together, the observed lung cancer mortality in relation to that expected was statistically significant (observed/expected = 2.419, $P < 0.001$). For the individual plants, the observed/expected ratio was not significant (observed/expected = 1.00, with 5 observed and 4.98 expected; $P < 0.44$) at the Bolton plant while it was significant ($P < 0.001$) at the Eaglescliffe plant (observed/ expected = 2.156, with 36 observed and 16.20 expected) and the Rutherglen plant (observed/expected = 2.854, with 75 observed and 26.18 expected). It should be noted, however, that the cohort at the Bolton plant was relatively small (202 workers)--not large enough to be reasonably able to detect a difference between observed and expected lung cancer deaths. It should also be noted that the observed/expected nasal cancer mortality ratio was statistically significant ($P < 0.05$) at the Rutherglen plant. The authors were interested in determining if plant modifications affected the relative risk of disease in men in the earlier study by Bidstrup and Case (1956). The authors found that the observed/ expected ratio of lung cancer deaths decreased from 3.0 ($P < 0.01$) for those who worked before the plant modifications, to 2.0 ($P < 0.005$) for those who worked before and after the modifications, to 1.9 ($P < 0.290$) for those who worked after the modifications were completed.

Because of the confounding factors of age distribution of the workforce, duration of employment, duration of follow-up, and environmental influences, the authors did a multivariate analysis of the data. For each individual, the analysis compared the risks of developing lung cancer based on the following factors: duration of employment, duration of follow-up, calendar period of employment, factory, age at entry, and estimated degree of chromate exposure. The authors found the greatest contribution to the risk of lung cancer mortality to be that of duration of employment followed by duration of follow-up, calendar period of employment, entry age, and estimated degree of chromate exposure. In this study the authors reported that an earlier, unpublished report of the study cohort presented data concerning the smoking habits of 70% of these workers, who had completed a questionnaire. The results of this survey indicated that the percentage of heavy smokers was lower for the study cohort than that reported for England and Wales (Todd 1962). The authors concluded that the questionnaire responses did not provide evidence that the respondents were at greater risk of lung cancer due to to smoking than was the population as a whole. Such a conclusion must be considered questionable, however, considering that 30% of the cohort did not respond. Other studies have found that the percentage of smokers among nonrespondents to questionnaires is higher than among respondents (Doll and Hill 1964, Criqui et al. 1979).

Watanabe and Fukuchi (1975) followed a group of 136 chromate production workers who worked or had worked in a chromate production factory on Hokkaido Island, Japan. The criteria for inclusion in the cohort was that the worker must have been exposed for more than 9 years to chromium compounds. The follow-up period was 14 years, from 1960 to 1973. Eight cases of lung cancer and two possible cases of lung cancer were identified during the follow-up period. The authors did not state how the ten cases were identified. Seven of these ten cases had died during the observation period, including the two questionable cases. The dates and causes of the deaths were ascertained by the workers' death certificates and by hospital records. Based on national vital statistics data, the expected number of lung cancer deaths for this population would be

0.33. Thus the observed number of lung cancer cases is 21.2 times greater (if the 2 questionable cases are counted with the observed lung cancer deaths) or 15.2 times greater (if only the five certain cases of lung cancer are counted). Both observed numbers are significantly ($P < 0.05$) greater than expected, however.

Ohsaki et al. (1978) studied the incidence of lung cancer in a cohort of 67 active chromate workers and 487 retired chromate workers at a factory on Hokkaido Island in Japan. It is not known at this time whether this is the same factory as was studied by Watanabe and Fukuchi (1975). The average exposure was 22.8 years (10 to 36 years), with 133 workers exposed for >10 years. In this population, the authors diagnosed 10 patients with lung cancer, and determined from death records that an additional four cases had occurred. The incidence of lung cancer in these chromate workers was 658 per 100,000, as compared to 13.3 per 100,000 for the Japanese population ($P < 0.01$ as calculated by the CAG). (It is presumed that the latter rate applies to the male population, although the authors did not state this explicitly.) No correction was made in this study for smoking habits, even though all but two of the individuals with lung cancer were heavy smokers.

Sano and Mitohara (1978) reported that of 36 deceased chromate workers in Tokyo, 19 had died of cancer of the respiratory organs. Although this report merely related case histories, the authors maintained that it supported the risk of cancer associated with the chromate industry. Of particular interest in this report were the total metal analyses of two workers exposed to chromium who died of respiratory cancer. Along with excessive levels of chromium, there were elevated levels of nickel, cobalt, beryllium, vanadium, and manganese in the lungs, indicating exposure to other possible carcinogens.

Satoh et al. (1981) conducted a mortality and morbidity study of 896 workers engaged in the manufacture of chromium compounds for one or more years during the period 1918 to 1975 at a plant in Tokyo, Japan. It was reported that during the period 1934 to 1975, 84% of the chromium compounds manufactured were hexavalent and 16% were trivalent. The plant was closed in 1975; workers were followed until 1978 or until death. Data on the causes and dates of death were collected from death certificates or other "reliable written testimony." In addition to the 896 workers who were followed, 165 chromium workers were not included in the study due to a lack of "necessary information." All of the latter group were retired workers whose permanent residence and current status were unknown and whose vital status as of the end of 1978 could not be determined. Of these 165, approximately 80% had left chromium work prior to 1949, and for 65% the date of birth was unknown. The average number of years as a chromium worker for the 165 not included in the study was about 7 years, less than the 10-year average for the 896 workers who were included in the study. The authors analyzed the mortality data by four different time periods, 1918-49, 1950-59, 1960-69, 1970-78, and the overall time period 1918-78. They reported the observed and expected number of deaths and SMRs for various diseases, and found that there was an excess risk of lung cancer for each of the time periods (mortality ratio = 9.5 for the 1918-78 time period; $P < 0.005$). No excess risk of death from any other disease was found for any of the time periods or for the overall time period. Satoh et al. also analyzed the data by length of working experience (1-10 years, 11-20 years, and 21+ years) for the time periods 1950-59, 1960-69, and 1970-78. For lung cancer deaths, but not for deaths from "all other cancers," the ratio of observed to expected deaths increased by length of working experience.

Satoh et al. studied morbidity by examining health insurance records for the period from 1974 through 1977 to determine if any sickness occurred in the 81 chromium-exposed workers as compared with the 82 nonexposed workers in the plant during that period. The authors reported that although the numbers were small, there was no apparent difference between the exposed and the nonexposed groups in the number of cases for any major disease category. It should be noted that respiratory cancer and perforation of the septum are compensable and thus do not appear in the health insurance records. Three years after the end of the chromium exposure, all 94 workers who had been exposed for 1 to 28 years (average 14.9 years) were given a complete series of liver and kidney function tests. All values were reported to fall within the normal range characteristic of Japanese males.

Korallus et al. (1982) reported the lung cancer SMRs for two West German chromate-producing plants during the period from 1948 through 1979. The population of North Rhineland-Westphalia was used as the comparison group in calculating the SMRs. The respiratory cancer SMRs for both plants, Leverkusen and Uerdingen, 1.92 and 2.24 respectively, were both statistically significant ($P < 0.05$) for the period of the study. The authors reported that when the study period was divided into six five-year intervals (1948-52, 1953-57, 1958-62, 1963-67, 1968-72, 1973-77) and one two-year interval (1978-79) that the respiratory cancer SMRs for these intervals generally decreased in both plants over the period of the study. This decrease was rather inconsistent in the Uerdingen plant, however. Additionally, three subcohorts were defined: individuals with beginning of exposure prior to January 1, 1948 (Group I), individuals exposed before and after the "change in manufacture" (the change in manufacture began in 1948 and was completed in 1957 at Leverkusen and in 1963 at Uerdingen) (Group II), and individuals with at least half their exposure after the completion of the "change in manufacture" (Group III). The "change in manufacture" refers to the initiation of "no-lime" processing of the chrome ore--a change which is believed to have resulted in a reduction of the carcinogen risk. For both plants there was a clear drop in the lung cancer SMR from Group I to Group III. For Uerdingen, the lung cancer SMRs were 2.76, 2.60, and 0.96 for Groups I, II, and III. For Leverkusen, the corresponding lung cancer SMRs were 2.85, 1.97, and 0.54. In neither the Leverkusen plant nor the Uerdingen plant, however, were the SMRs for Groups I, II, or III significantly different ($P < 0.05$) from each other. Thus, the decrease in the respiratory cancer SMR from Groups I to III might be due to chance. A reduction in nasal perforations, symptomatic of chromium exposure, was also observed for Groups I to III. This latter finding is statistically significant for both plants at $P < 0.05$ (chi square test for linear trend in proportions), and would support a conclusion of a decrease in chromium exposure from Group I to Group III.

7.2.2.2. CHROME PIGMENT WORKERS -- Two mortality studies in which workers were exposed only to hexavalent chromium have been conducted in the chrome pigment industry. Langard and Norseth (1975) reported on three pigment plants in Norway that were in operation between 1948 and 1972. One of the plants, however, was brought on line only in 1972, the year the study ended. Between these dates, 133 workers were identified as being employed at the three plants. Of the 133, 24 had been employed >3 years, and of this cohort, six cases of cancer (three of lung cancer and one of gastrointestinal cancer) were identified through the Cancer Registry of Norway. All three of the lung cancer cases had been employed 5 years or longer. Two other cases, one with prostate cancer and one with nasal cancer, were identified among the 133 workers. These cases did not qualify for membership in the cohort employed for >3 years, however. Data from the Cancer Registry indicated an expected number of lung cancer cases among those employed of 0.079; thus, the observed number of cases was 38 times that expected. Exposure levels as determined by personal monitoring were reported for the plants for the year 1972, the year in which the study ended, with chromium levels in the two older plants ranging between 0.04 and 1.35 mg/m^3, and levels in the new plant between 0.01 and 0.08 mg/m^3. The distribution of the number of employees per year was not presented, although it was indicated tht only seven or eight employees worked in the plants between 1948 and 1950, with this number increasing slowly to a level of 30 workers by 1972. Although an increased risk of lung cancer was indicated, two of the individuals with lung cancer were moderate to heavy smokers. Nevertheless, a relative risk of lung cancer of 38 would not be explained by differences in smoking between the study cohort and the Norwegian population.

Davies (1978, 1979) studied three chromate pigment plants in England, of which plants A and B produced both zinc and lead chromate, while plant C produced only lead chromate. The cohort of exposed workers consisted of employees with ≥ 1 year of service, who were first hired between 1933 and 1967 for plant A, 1948 through 1967 for plant B, and 1946 through 1961 for plant C (these years were governed by the availability of complete employment records), and for whom vital statistics were available as of 1977. Using these guidelines, 396, 136, and 114 subjects were obtained from plants A, B, and C, respectively. These groups were further subdivided into high and medium exposure and low exposure groups. The observed mortality from lung cancer in the different plants by exposure category was compared to the expected mortality as calculated from national lung cancer mortality rates for all males in England and Wales. These data are presented in Table 7-16. The exposure categories of high and medium were combined, the author stated, because they were "similar." No details

TABLE 7-16. LUNG CANCER IN WORKERS IN THE CHROMATE PIGMENT INDUSTRY
(Davies 1979)

	High and medium exposure			Low exposure		
Plant and year of initial employment	Number of men	Observed lung cancer	Expected lung cancer	Number of men	Observed lung cancer	Expected lung cancer
Plant A						
1932 - 1954	175	18[b]	8.17	77	2	2
1955 - 1967[a]	62	0	1.14	14	0	0.16
Plant B						
1948 - 1967	116	7[c]	1.43	20	0	0.1
Plant C						
1946 - 1967	95	1	2.46	19	1	0.37

[a] Plant modification in Plant A in 1955 considerably reduced employee exposure to chromates. Thus, results were divided into two time periods, 1932-54 and 1955-67, for the purpose of analysis.

[b] $p < 0.01$.

[c] $p < 0.001$.

were given in this regard, but it is presumed the author meant that the categories were similar with regard to the ratios of observed to expected lung cancer deaths. Adjustments to the expected number of lung cancer death values were made in the following manner: (1) the expected number of lung cancer cases was adjusted upward because the proportion of unskilled and semiskilled workers in the study population was higher than in the general population, and these persons are known to smoke more than the national average; (2) the expected number was adjusted downward for plant B and upward for plant C to reflect the respective differences in local lung cancer mortality in comparison to the national lung cancer mortality. The author did not state how these adjustments were calculated. An elevated risk of lung cancer was present only in the combined high and medium exposure group in plants A and B, while plant C, which manufactured only lead chromate, showed no elevated risk. Also, workers in plant A who had been hired after production modification in 1955 showed no increased risk of lung cancer, even though there was a minimum followup period of 15 years. The authors suggested that these data indicate that zinc chromate was associated with the etiology of lung cancer, while lead chromate was not, and although the data were limited by the small sample size, the authors claim that engineering controls had effectively lowered the risk of lung cancer in plant A.

Frentzel-Beyme (1983) reported that the observed number of lung cancer deaths exceeded those expected among workers in five chromate pigment plants in the Netherlands and West Germany. In only one factory, however, was this excess statistically significant. The authors did not find a lung cancer mortality dose-response by intensity of exposure or duration of exposure. The numbers of deaths in each exposure category were rather small, however.

7.2.2.3. CHROME PLATING WORKERS -- Royle (1975) studied mortality in the chromium plating industry of England in a retrospective study between 1969 and 1972, and also reported on the first 2 years of a prospective study that began in 1972. Workers in this industry are exposed to hexavalent chromium in the form of chromic acid mist and some sodium dichromate dust. In the retrospective study, 1,238 chrome plating workers employed for >3 months were traced along with 1,284 manual laborers used as controls. The control subjects were matched to the exposed workers for sex and the last date they were known to be alive, while the subgroup of workers who were currently employed in the chrome plating industry were also matched for smoking habits. Similar success was achieved in tracing both groups, and from the response to questionnaires, there was little difference in the smoking habits of the groups. The death rate was higher in the chrome plating group, with 109 deaths observed as compared to 85 in the control group. In examing cause-specific deaths, there was a significant ($P < 0.05$) difference in the death rate for cancer at all sites, 3.15% in chrome platers as compared to 1.63% in controls; while deaths from malignancy of the lung and from malignancy of the gastrointestinal tract were each increased, although not significantly. Other causes of death were similar in the two groups. In a small group (220 subjects) with high exposure, there was greater mortality associated with employment of 1 year or more as compared with exposure for less than 1 year. The results of the first 2 years of the prospective study indicate an increased proportionate cancer mortality with 12 cancer deaths (the tables indicate 12, although the text reports 9) of 33 deaths reported in the chrome-exposed group, compared with 3 cancer deaths of 19 deaths in the control group.

In addition to the mortality study, Royle also conducted a morbidity study of the chrome plating workers. The controls were the same as those in the mortality study. The author stated that detailed results of the morbidity study would be published in a separate article. Among platers, it was reported that there was a significant increase in the prevalence of a large majority of different respiratory symptoms. The possible causes of this increase were examined in some detail. In the course of the investigation, it was found that a significantly larger proportion of controls (8.3%, 93 controls) than platers (3.6%, 36 platers) had been engaged in asbestos processing. Thus, the risk of lung cancer due to chromium exposure in platers as compared to that of the controls may have been underestimated. The results of this study were inconclusive because of the relatively short (3-year) follow-up period in this retrospective study, and because results from the prospective study are only preliminary.

Okubo and Tsuchiya (1979) conducted a cohort study of 889 Tokyo chrome platers, with an unspecified number of controls selected from the same factories as the chromium platers. The follow-up period was April 1, 1970 to September 30, 1976. Vital statistics were ascertained using the records of the Tokyo Health Insurance Society of the Plating Industry. The type of work and chromium exposure history of the members of this society were investigated by means of a questionnaire sent to the manager of each factory. The recovery rate of the questionnaire was 70.5%. Survival information on retired subjects was obtained from the offices of the Japanese family registration system. Among the 889 male chromium platers, 19 deaths were observed, or about 50% of those expected. The expected number of deaths was calculated using the annual male mortality rates, by age, for Tokyo. In contrast, the authors reported a slightly higher percentage of deaths in the control group.

The authors noted that two possible types of error may have occurred in this study: 1) deaths from the chromium group may have been incorrectly assigned to the control group, and 2) the 30% who were nonresponders may have represented a significant number of factories in which chromium-related deaths occurred.

In addition to the problems noted by the authors, the follow-up period for this study, six years, was probably not long enough to be able to detect differences in lung cancer mortality resulting from chromium exposure. Also, the size of the cohort, 889, was relatively small for the detection of significant differences in lung cancer mortality.

Silverstein et al. (1981) found a statistically significant increase ($P < 0.001$) in the lung cancer proportionate mortality ratios for both male and female white employees in a die-casting and electroplating plant. In this plant, workers were exposed to chromium during electroplating, but nickel and copper were also used in electroplating. The other operations of the plant were zinc alloy die-casting and buffing, polishing, and cleaning of zinc and steel parts. Because of the employees' exposure to other potential carcinogens, no conclusion can be made from this study regarding the association of chromium electroplating and lung cancer mortality.

7.2.2.4. FERROCHROMIUM WORKERS -- Pokrovskaya and Shabynina (1973) studied cancer mortality among workers at a chromium ferroalloy plant in the Soviet Union for the period 1955-1969. Deaths among the workers were identifed through the archives of the city registrar's office. Age-specific mortality rates for the plant employees were compared with the corresponding age-specific mortality rates for persons in the city where the plant was located. Persons who were exposed to chromium in other occupational settings were excluded from the comparison group.

Workers in the plant were reported to be exposed to low-solubility chromium compounds. The valence of the chromium and the characteristics of the chromium exposure (dust or aerosol) varied throughout the different sections of the plant. The greatest concentration of chromium in the air was noted during the smelting of refined ferrochromium. In addition to chromium, the authors reported that large amounts of "tarry substances" entered the work area, together with furnace gases, during the smelting process. These substances included benzo[a]pyrene, which is formed during the caking of the electrode mass. The highest concentrations of tarry substances were observed at the work stations of electrode workers; a significantly lower concentration was observed at the work stations of smelters and batchers.

The mortality ratios for cancer of all sites and for lung, stomach, and esophageal cancer for the ferroalloy production workers are reported in Table 7-17.

TABLE 7-17. MORTALITY RATIOS RESULTING FROM MALIGNANT TUMORS AMONG WORKERS IN CHROMIUM FERROALLOY PRODUCTION
(adapted from Pokrovskaya and Shabynina 1973)

	Relative risks of cancer mortality							
	All sites		Lungs		Stomach		Esophagus	
Age groups	Males	Females	Males	Females	Males	Females	Males	Females
30-39	2.6	2.8	4.4	-	3.8	-	-	-
40-49	0.5	1.3	-	-	0.8	4.0	-	-
50-59	3.3[a]	7.9	6.6[a]	-	3.2	-	2.0[a]	-
60-69	2.0	-	-	-	-	-	11.3[a]	-

[a] P=0.001.

As can be seen from the table, the mortality ratio for all malignant tumors was higher for the ferroally workers in almost all age groups of both sexes. The mortality ratio (MR) for lung cancer was significantly higher (MR = 6.6, P = 0.001) among males in the 50-59 year age group and was 4.4 among males in the 30-39 year age group. (The statistical significance of this latter mortality ratio was not reported.) The mortality ratio for esophageal cancer was significantly higher (P = 0.001) among males in the 50-59 and 60-69 year age groups (RR = 2.0 and 11.3, respectively).

The average age of workers in ferrochromium production who died of cancer was reported to be significantly lower than that of the city residents who died of cancer--49.4 and 62.9 years, respectively. A higher level of cancer mortality was also reported among workers subjected to the greatest dust load (charge loaders, metal breakers, and smelters). The authors reported a high mortality rate from cancer among workers in the charge preparing and finishing sections, where high chromium-containing dust pollution was observed but no exposure to benzo[a]pyrene was found. This study appears to be merely a comparison of cancer mortality between the ferroalloy plant workers and the local population for the time period 1955-1969. Very little detail was provided by the authors. No cohort was defined. The number of person-years and the number of cancer cases among the ferroalloy workers were not reported; nor were the number of cases and and the number of individuals in the comparison population. Because of the sketchiness of the reporting and the lack of an adequately defined cohort, the results of this study are open to question. In addition, if a high turnover rate existed among employees of the plant, the results of the study could be misleading.

Langard et al. (1980) studied ferrochromium workers at a ferrochromium plant in Norway who were predominantly exposed to trivalent chromium. In an industrial hygiene study of the plant in 1975, ambient chromium levels of between 0.01 and 1.34 mg/m^3 were detected in the ferrochromium department, and, of this chromium, it was determined that 11% to 33% was hexavalent. The study consisted of 976 employees who had worked for >1 year, were alive after 1953, and had been initially employed prior to 1960. The study was divided into 10 subgroups by job description, with only 325 subjects specifically associated with ferrochromium production and considered exposed to chromium. Comparison of cancer incidence for all sites and for different sites were made between the Norwegian male population and the ferrochromium worker population, using the Norwegian Cancer Registry. Poisson distribution was used to test for statistical significance. A comparison of total mortality was also made. Of the 10 job-related subgroups, only the ferrochromium workers had a significant difference between the observed and expected number of "lung" cancer cases (7 observed versus 3.1 expected, $P < 0.05$). (Note: The statistical significance was calculated by Langard et al. to be $P = 0.08$. The CAG tested the difference using the Poisson distribution, and found the significance to be $P < 0.05$). There is a problem with the authors' use of the term "lung cancer." Although the authors primarily refer to "lung cancer" in the text, they also use the terms "cancer of the respiratory tract" and describe the "lung cancer" cases in one of the tables as being of International Classification of Disease (ICD) codes 162 and 163. ICD codes 162 and 163 include cancer of the respiratory tract other than lung cancer. This ambiguity raises some question as to the authors' comparisons of observed and expected cases. If the expected number of cases is calculated for ICD codes 162 and 163, and the observed number of cases are only lung cancer cases, then the relative risk of lung cancer has been underestimated. If the opposite is true, then the risk has been overestimated. If the observed number of "lung cancer" cases mistakenly includes cases of mesothelioma, then the stated "lung cancer" risk due to chromium may instead be a reflection, at least partially, of asbestos exposure. This ambiguity must therefore be considered when interpreting the results.

Total mortality and cancer incidence at all sites were similar to the general population. The relative risk of "lung cancer" among the ferrochromium workers as compared to the Norwegian male population may have been underestimated, however, since the county in which the plant was located, Hordaland, had an age-adjusted "lung cancer" incidence that was 58% of Norway's "lung cancer" incidence rate. If this 58% is multiplied by the expected number of "lung cancer" cases calculated from national rates, the newly calculated expected number differs significantly from the observed number of cases ($P < 0.01$). If non-chromium-exposed workers in this plant had been used as a control population, the risk of "lung cancer" in chromium-exposed workers would have increased to 8.5, which is significant at $P < 0.01$. The ferrochromium workers were possibly exposed to two other carcinogens, asbestos and polycyclic aromatic hydrocarbons; however, this was unlikely to have been an important factor, the authors indicated, since a group of 243 ferrosilicon workers in the same plants were believed to have been exposed to these two known carcinogens to the same degree, and no increased risk of "lung cancer" (0 observed and 2.78 expected) was observed among these workers. However, the sample size for the ferrosilicon workers (number = 243) would have to be considered too small to be able to detect any significant excess of "lung cancer."

In studies of the ferrochromium industry in Sweden, Axelsson et al. (1980) concluded that there was no association between employment in the ferrochromium industry and risk of respiratory cancer. The study cohort consisted of 1,876 men who had been employed for one or more years between 1930 and 1975, and who were alive as of 1951. Observed cases were included for comparison if they occurred 15 years after first exposure. The exposed population was compared with males in the county in which the plant was located, and comparisons were tested for significance by two-sided P-values using the Poisson distribution. The workers were subdivided into four groups consisting of arc-furnace workers; workers in transport, metal grinding, and sampling; maintenance workers; and office workers. It was estimated that these groups had been respectively exposed to 2.5, 0.5 to 2.5, 2.5, and 0 mg/m^3 of trivalent chromium and elemental chromium, and 0.25, 0.01 to 0.05, 0.05, and 0 mg/m^3 of hexavalent chromium, respectively. Medical examination of employees during the last 3 years of the study detected three cases of perforated septum of the nose, suggesting that some exposure to hexavalent chromium had occurred in at least a portion of the work force. No statistically significant difference in cancer mortality between that observed in the workers and that expected based on national mortality data was found. The only significant increase in cancer incidence was an increase in respiratory cancer (4 observed and 1 expected, $P = 0.038$) in the 315 maintenance workers. Of the four cases of respiratory cancer, two were diagnosed as mesotheliomas, and the authors suggested that these cases may have resulted from exposure to asbestos. It was also noted that the control population was mainly rural dwellers, while the exposed group consisted of urban dwellers, and that rural residents in Sweden generally smoked less. From the results of this study, the authors concluded that no association existed between exposure to predominantly trivalent chromium and elemental chromium and the development of cancer. Because of the confounding effects of smoking and exposure to asbestos, no definite conclusions can be drawn from this study.

7.2.3. Quantitative Estimation. This quantitative section deals with the unit risk for chromium in air and the potency of chromium relative to other carcinogens that the CAG has evaluated. The unit risk estimate for an air pollutant is defined as the incremental lifetime cancer risk over the background occurring in a hypothetical population in which all individuals are exposed continuously to a concentration of 1 ug/m^3 of the agent in the air that they breathe. This calculation is done to estimate in quantitative terms the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: 1) to compare the carcinogenic potency of several agents with each other, and 2) to give a crude indication of the population risk which might be associated with exposure to these agents, if the actual exposures are known.

The data used for quantitative estimation can be of two types: 1) lifetime animal studies, and 2) human studies where excess cancer risk has been associated with exposure to the agent. It is assumed, unless evidence exists to the contrary, that if a carcinogenic response occures at the dose levels used in a study, then responses will also occur at all lower doses, with an incidence determined by an extrapolation model.

There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards. For practical reasons such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time the dominant view of the carcinogenic process involves the concept that most cancer-causing agents also cause irreversible damage to DNA. This position is reflected by the fact that a very large proportion of agents that cause cancer are also mutagenic.

There is reason to expect that the quantal type of biological response, which is characteristic of mutagenesis, is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence from mutagenesis studies with both ionizing radiation and a wide variety of chemicals that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The low-dose linearity and nonthreshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxins in the diet). There is also some evidence from animal experiments that is consistent with the linear nonthreshold model (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the linear nonthreshold model has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship.

The quantitative aspect of carcinogen risk assessment is included here because it may be of use in the regulatory decision-making process, e.g., setting regulatory priorities, evaluating the adequacy of technology-based controls, etc. However, it should be recognized that the estimation of cancer risks to humans at low levels of exposure is uncertain. At best, the low-dose linearity extrapolation model used here provides a rough but plausible estimate of the upper limit of risk; i.e., it is not likely that the true risk would be much more than the estimated risk, but it could very well be considerably lower.

The risk estimates presented below should not be regarded as accurate representations of the true cancer risks even when the exposures are accurately defined. The estimates presented may, however, be factored into regulatory decisions to the extent that the concept of upper risk limits is found to be useful.

There are many epidemiologic studies demonstrating that hexavalent chromium (Cr VI) is a potential human carcinogen, but few of these studies provide adequate exposure data for use in risk estimation. One study by Mancuso (1975) provides what the CAG feels is limited but adequate information for this purpose, however. Mancuso's data is used as the main data base for estimating the carcinogenic potency of hexavalent chromium. For comparison, data from three foreign studies on ferrochromium plants are also used in the potency calculations. From the quantitative risk assessment viewpoint, these studies are less adequate than the Mancuso study. For the Norwegian study (Langard et al. 1980), the exposure measurements were taken in 1975, while some workers could have been exposed to chromium as early as 1928, when the ambient dust levels were much higher than in recent years. For the Swedish study (Axelsson et al. 1980), the chromium-exposed workers did not show a significant increase of lung cancer, and thus only the statistical upper bound of the response can be used in potency estimation. For the above reasons, it is expected that the use of data from the Norwegian and Swedish studies would result in an overestimation of the true carcinogenic potency of hexavalent chromium. While the Russian study (Pokrovskaya and Shabynina 1973), does not have the deficiencies of the other two foreign studies, the cohort in this study is not well defined, and thus the validity of the data reported is open to question. In an effort to provide alternative potency estimates, the data from these less adequate studies have also been used by the CAG to calculate the potency of hexavalent chromium. The potency calculated on the basis of Mancuso's data is consistently smaller than (but within 5 folds of magnitude of) the lower-limit estimates calculated from the three foreign studies.

Animal data from intratracheal studies have not been used to estimate the carcinogenic potency of chromium by inhalation because there is no pharmacokinetic information relating the distribution of chromium to lung tissues by inhalation and by intratracheal administration. This information is needed because the dose distribution is clearly different between these two exposure patterns. Furthermore, the physiological mechanism of dose distribution by intratracheal administration may depend (in a non-linear fashion) on the dose levels used in the experiment, as evidenced by the observation that a single administration of sodium dichromate induced a carcinogenic response in Sprague-Dawley rats but failed to induce a response when the same weekly dose was given over 5 days.

7.2.3.1. ESTIMATION OF THE CARCINOGENIC PPTENCY OF HEXAVALENT CHROMIUM (Cr VI) BASED ON THE MANCUSO (1975) DATA -- The Mancuso study was based on a cohort of 332 white male workers who were employed in a chromate plant between 1931 (when the plant began to operate) and 1937, and who were followed to 1974. In his study, Mancuso reported lung cancer death rates by levels of exposure to soluble, insoluble, and total chromium concentrations. Because only lung cancer mortality for total chromium exposure was reported by age group, the CAG has used only the dose-response data for total chromium to estimate the carcinogenic potency of hexavalent chromium. Although the use of dose-response data for total chromium will result in an underestimation of the potency of hexavalent chromium, we believe that the effect of this underestimation is approximately compensated for by other factors that may overestimate the risk. These issues will be discussed further in the pages that follow.

Exposure information in the Mancuso study was derived from an industrial hygiene study of the plant conducted in 1949. In this study, time-weighted averages of exposure to insoluble, soluble, and total chromium per cubic meter were calculated for each occupation and for each worker in every department. Using these data and company personnel records, Mancuso was able to calculate an estimate of exposure to soluble, insoluble, and total chromium by duration of exposure (in mg/m^3-years) for each member of the 1931-37 cohort. In 1949, after the industrial hygiene study had been conducted, the company initiated a comprehensive program designed to reduce employees' exposures and improve manufacturing efficiency. Until that time, however, the company had not undertaken any programs for the purpose of reducing employee exposure. It should be noted, however, that Bourne and Yee (1950), who conducted the industrial hygiene survey in 1949, reported that "in order to meet price and quality competition, improvements in equipment and processes have been made periodically during the past 18 years, and it is the universal experience of industrial hygiene personnel that greater process efficiency is almost invariably associated with a more healthful working environment. Therefore, there seems little doubt that atmospheric contamination in the past was greater than in 1949." Nonetheless, no concerted effort was made to reduce employee exposure until late in 1949, and because this particular plant was a relatively modern one at the time of the industrial hygiene survey, it is unlikely that improvements in efficiency over the period 1931 to 1949 would have reduced employee exposure to a great extent. Thus, the CAG considers Mancuso's data to be a reasonable approximation of what workers in the study cohort were exposed to during their entire working history. The CAG recognizes the possibility that the exposure may be slightly underestimated because of the likelihood that a greater proportion of the "total exposure" was contributed prior to 1949 than post-1949.

The effects of underestimating the exposure concentration, as well as the effects of other uncertainties on the estimation of potency, will be addressed in the Discussion section.

7.2.3.1.1. Data Available for Potency Calculations -- Table 7-18, which is taken directly from Mancuso (1975), presents age-specific lung cancer deaths, corresponding person-years, and range of exposures to total chromium.

To estimate the lifetime cancer risk due to exposure to chromium, it is assumed that an exposure, D (mg/m^3-years), as presented in Table 7-18, is equivalent to the continuous exposure d (ug/m^3) calculated by

$$d = \frac{D}{fL_e} \times \frac{8}{24} \times \frac{240}{365} \times 10^3 \text{ ug/m}^3$$

where L_e is the midrange in each age category, f is the fraction of time in age exposed, and 8/24 and 240/365 are the fractions of a day and year, respectively, that a worker spent at the plant. For instance, if D = 8 mg/m^3-years, $L_e = 60$, and f = 0.65, then d = 44.96 ug/m^3. The assumption of f = 0.65 implies that the cohort exposure to chromium began approximately at age 20. The assumption is that the particular exposure pattern (unknown to us) leading to the cancer mortality rates as observed is equivalent to the continuous constant exposure starting from the age when exposure began. This assumption may or may not be realistic. However, it would be more unrealistic to make a different assumption concerning the exposure pattern when all that is given is an exposure which itself was calculated by taking the weighted average of the duration of exposure for each respective job the worker had.

Since the person-year in each category presented in Table 7-18 is very small, the exposure categories are combined as shown in Table 7-19 to increase statistical stability. The last column of Table 7-19 is given for the purpose of identifying which exposure categories in Table 7-18 are combined. The midrange of age and exposure concentration is used in Table 7-19. Data in this table are used to estimate the lifetime cancer risk due to chromium exposure.

TABLE 7-18. AGE-SPECIFIC LUNG CANCER DEATHS AND GRADIENT EXPOSURES TO TOTAL CHROMIUM (Mancuso 1975)

		Exposure to total chromium (mg/m^3-year)						
Age		<1.00	1.0-1.99	2.0-3.99	4.0-5.99	6.0-6.99	7.0-7.99	8+[a]
45-54	Deaths	1	2	2	4	3	3	0
	Person-years	886	459	583	348	159	140	262
55-64	Deaths	1	3	1	4	2	3	1
	Person-years	707	356	462	250	113	98	203
65-74	Deaths	1	1	2	1	1	0	3
	Person-years	235	166	182	80	42	41	81

[a] Data in the last column are not used in the CAG's risk assessment because the range of exposure in this class is not known, and it does not appear reasonable to assume that all three age groups had an identical exposure distribution in this class.

TABLE 7-19. COMBINED AGE-SPECIFIC LUNG CANCER DEATH RATES AND TOTAL CHROMIUM EXPOSURE (in ug/m^3)

Age	Concentration (ug/m^3)[a]	Deaths	Person-years	Background rate[b]	Exposure range as presented in Table 7-18
50	5.66	3	1345	6.05×10^{-4}	$\leq$ 1.99
50	25.27	6	931	6.05×10^{-4}	2.0 - 5.99
50	46.83	6	299	6.05×10^{-4}	6.0 - 7.99
60	4.68	4	1063	1.44×10^{-3}	$\leq$ 1.99
60	20.79	5	712	1.44×10^{-3}	2.0 - 5.99
60	39.08	5	211	1.44×10^{-3}	6.0 - 7.99
70	4.41	2	401	1.57×10^{-3}	$\leq$ 1.99
70	21.29	4	345	1.57×10^{-3}	2.0 - 7.99

[a] The midrange of each exposure category in Table 7-18 is first converted to ug/m^3 by using $f = 0.65$ in the formula described in the section "Data Available for Potency Calculations." The concentrations presented in this table are the averages of several exposure categories weighted by corresponding person-years.

[b] Background rate is estimated from 1964 U.S. Vital Statistics. The year 1964 is selected because it is estimated that a large proportion of lung cancer deaths occurred during that year.

7.2.3.1.2. Choice of Dose-Response Model -- It has been widely recognized (e.g., Doll 1971) that the age-specific incidence curve tends to be linear on doubly logarithmic graphs, or equivalently, the age-specific incidence follows the mathematical form

$$I(T) = bT^{k-1}$$

where b and k are parameters that may be related to other factors such as dose, and T may be one of the following three cases:

1. T is age when cancer is observed,
2. T is the time from the first exposure to observed cancer, or
3. T is the time from exposure to cancer minus the minimum time for a cancer to be clinically recognized.

This model has been shown to arise from the somatic mutation hypothesis of carcinogenesis (Armitage and Doll 1954, Whittemore 1978, Whittemore and Keller 1978). It has also been shown to arise from the epigenetic hypothesis when the reversible cellular change is programmed to occur randomly (Watson 1977). These authors and many others have used this model to interpret and/or estimate potency from human data.

Since the data that could be used for risk estimation are limited, a simple model that fits the data should be used. Therefore, the observed age-specific incidence is assumed to follow the model

$$I(t,d) = B(t) + h(t,d)$$

where B(t) is the background rate at age t and $h(t,d) = Q(d)\ t^{k-1}$ with $Q(d) = q_1 d + q_2 d^2$, a function of dose d.

Once the parameters q_1, q_2, and k are estimated, the lifetime cancer risk associated with an exposure d by age t, taking into account the competing risk, can be calculated by

$$P(t,d) = \int_0^t h(s,d) \exp \left\{ -\left[\int_0^s h(y,d)dy + A(s) \right] \right\} ds$$

where $\exp[-A(s)]$ is the probability of surviving to age s and $h(t,d) = I(t,d) - B(t)$, the age-specific incidence after adjusting the background rate.

7.2.3.1.3. Estimation of the Risk Model -- To estimate the parameters in $h(t,d)$ we assume, as is usually done, that the number of lung cancer deaths, X, at age t, follows the Poisson distribution with the expected value

$$E(X) = N \times (B + Q(d)\, t^{k-1})$$

where N is the person-year associated with X, B is the background rate at age t, and $Q(d) = q_1 d + q_2 d^2$.

Using the BMDP computer program P3R and the theory relating the maximum likelihood and non-linear least square estimation by Jennrich and Moore (1975), the parameters q_1, q_2, and k are estimated by the method of maximum likelihood as $q_1 = 1.11 \times 10^{-7}$, $q_2 = 1.84 \times 10^{-9}$, and $k = 2.915$; the corresponding standard deviations are respectively 7.8×10^{-7}, 1.2×10^{-8}, and 1.7.

Thus, the age-specific cancer death incidence at age t due to chromium exposure d ug/m^3 is given by

$$h(t,d) = Q(d)\, t^{1.915}$$

where

$$Q(d) = 1.11 \times 10^{-7} d + 1.84 \times 10^{-9} d^2$$

The model fits the data well, as can be seen from the goodness of fit statistic

$$X^2 = \Sigma\, (O-E)^2/E = 1.60$$

which has, asymptotically, a chi-square distribution with 5 degrees of freedom under the model specified. The observed and predicted values used in calculating X^2 are (3, 2.5), (6, 7.2), (6, 5.1), (4, 3.1), (5, 6.7), (5, 4.1), (2, 1.4) and (4, 4.3).

Taking into account the competing risk, the lifetime probability of lung cancer death due to exposure to chromium d ug/m^3 is given by

$$P(L,d) = \int_{o}^{L} h(t,d)\exp\left\{-[(Q(d)/2.915)\ t^{2.915} + A(t)]\right\}dt$$

where L is the maximum human lifetime and is mathematically equivalent to infinity, since the probability of surviving beyond L is 0.

At low doses, approximately,

$$P(L,d) = d \times P(L,1)$$

where P(L,1) is the lifetime cancer risk due to exposure to 1 ug/m^3 of chromium. The unit risk, P(L,1), has been adopted by the CAG as an indicator of the carcinogenic potency of a chemical compound.

7.2.3.1.4. Calculation of the Risk at 1 ug/m^3 -- To calculate the unit risk, P(L,1), it is necessary to know exp[-A(t)], the probability of surviving to age t. Since this probability can only be estimated, it is assumed that the survival probability is constant over a 5-year interval, as provided in the U.S. Vital Statistics.

Using this approximation and by integrating the formula P(L,1), we have

$$\begin{aligned} P(L,1) &= \Sigma[\exp(-3.87 \times 10^{-8}\ t_{i-1}^{\ 2.915}) - \exp(-3.87 \times 10^{-8} t_i^{\ 2.915})] \times P_i \\ &= 1.16 \times 10^{-2} \end{aligned}$$

where (t_{i-1}, t_i) is a 5-year interval and P_i is the probability of survival up to the age t_{i-1}. P_i is assumed to be a constant over the interval and is estimated from the 1975 U.S. Vital Statistics.

7.2.3.1.5. Alternative (Crude) Approach for Calculating the Carcinogenic Potency of Chromium from the Mancuso (1975) Data -- As a crude approximation, the carcinogenic potency of chromium can be calculated by $B = (R-1) \times P_0/d$, where $P_0 = 0.036$ is the estimated lung cancer mortality rate for the U.S. population, R is the relative risk of the lung cancer deaths in the cohort, and d is the "standardized" lifetime dose concentration to which the workers were assumed to be exposed. This approach is used by the CAG to calculate carcinogenic potency when the only data available are the relative risk estimate and an average exposure concentration.

For the Mancuso (1975) data, the relative risk R and the "standardized" dose d are estimated respectively to be $R = 7.2$ and $d = 15.5$ ug/m^3. They are calculated by combining the relative risks and dose concentrations in each of the age-exposure categories, weighted by the relative magnitude of person-years, as shown in Table 7-19.

Therefore, the carcinogenic potency of hexavalent chromium (Cr VI) is estimated to be

$$B = (7.2-1) \times 0.036/15.5 = 1.4 \times 10^{-2}/\text{ug/m}^3.$$

This crude estimate is only slightly higher than the previous estimate, 1.2×10^{-2}/ug/m^3.

7.2.3.1.6. Discussion -- The following discussion is intended to provide some insight about the uncertainties of estimating the carcinogenic potency of hexavalent chromium on the basis of the Mancuso (1975) data.

1. As noted previously, the risk of hexavalent chromium is estimated on the basis of the total chromium obtained from all the soluble and insoluble

chromium to which workers were exposed. Since only some compounds of hexavalent chromium are known to be carcinogenic, the potency presented above is likely to be underestimated. This underestimation seems unlikely to be more than sevenfold (or smaller) on the basis of Bourne and Yee (1950). Bourne and Yee reported that the ratios of trivalent chromium (Cr III) and hexavalent chromium (Cr VI) concentrations in the airborne dust in nine major departments in the plant ranged from 1 to 3 except for two departments where the ratios were 6 for the lime and ash operation and 52 for the ore preparation. Excluding the ore operation, the maximum ratio of trivalent chromium and hexavalent chromium is 6, and thus the underestimation of the risk would not be more than sevenfold.

2. As indicated previously, there is a possibility that the use of 1949 hygiene data may result in a slight underestimation of what workers were actually exposed to. However, because the plant was relatively modern at that time, the underestimation is unlikely to be very considerable. If an underestimation of 2 times were assumed, then the unit risk would be reduced from 1.2×10^{-2}/ug/m^3 to 6.0×10^{-3}/ug/m^3.

3. The risk presented in the present report may be somewhat overestimated in the sense that it is implicitly assumed that the smoking habits of chromate workers were similar to the general white male population, while it is generally accepted that the proportion of smokers is higher for industrial workers (thus the higher background incidence rates) than for the general population. As a sample calculation, it was found that if the background rate of lung cancer mortality for the cohort in Table 7-19 is increased by 40%, then the corresponding unit risk would be reduced by about 25%, or from 1.2×10^{-2} to 8.7×10^{-3}.

The background age-specific rate of lung cancer at ages 50, 60, and 70 could be 40% more than those presented in Table 7-19, should it be assumed that 80% of chromate workers are ever-smokers (individuals who smoke at least 100 cigarettes during their lifetimes) and only 50% of the general white male population are ever-smokers. It could also result from other assumptions about the smoking habits of the chromate workers and the general population. For instance, the background rate could be increased by approximately 40%, based on the age-specific cancer rates provided by Doll (1971), if the proportion of smokers in each smoking level is distributed as follows:

NUMBER OF CIGARETTES SMOKED PER DAY

	0	1-14	15-24	25 or more
Chromate workers	0.3	0.2	0.3	0.2
General population	0.5	0.2	0.2	0.1

Other reasonable assumptions about the smoking habits of the cohort workers would not reduce the risk estimate by more than 50%. Therefore, it is unlikely the risk is overestimated by more than four times, considering both the smoking habits and the underestimates of exposure by a factor of two.

7.2.3.2. POTENCY ESTIMATION BASED ON LANGARD ET AL. (1980) -- The study population consisted of 976 employees of a ferrochromium plant in Norway who worked for at least one year, were alive after 1953, and were initially employed prior to 1953. All members of the study population were considered "under observation" from the beginning of 1953 until 1977 inclusively, or in the case of later initial employment, from one year after employment in the plant. A subgroup of 325 workers were identified as specifically associated with ferrochromium production and considered exposed to chromium. The relative risk of lung cancer in chromium-exposed workers was estimated to be 8.5 when non-chromium-exposed workers in the same plant were used as a control population.

The authors considered the use of this control group more appropriate than the other reference populations because both chromium-exposed and non-chromium-exposed workers were similar with respect to the factors that could influence lung cancer response. The chromium concentration to which the workers were exposed is not available. In a complete industrial hygiene survey carried out during 1975, the ambient chromium levels in the plant were found to be between 0.01 mg/m^3 and 1.34 mg/m^3, and of this chromium, it was determined that 11% to 33% was hexavalent. Clearly, the measurements taken in 1975 underestimate the actual chromium ambient levels to which most of the workers were exposed. These concentrations are used in our potency calculations, with the understanding that the potency so estimated can only be considered an upper-bound estimate.

Assuming that the hexavalent chromium content in the sample was 19% (i.e., the geometric mean of 11% and 33%), the hexavalent chromium ambient concentrations ranged from 1.9 ug/m^3 to 254.6 ug/m^3. These concentrations are "standardized" to the lifetime exposure, 0.1 ug/m^3 and 14.0 ug/m^3, as calculated by the formula

$$d \times (8/24) \times (240/365) \times (\ell/L)$$

where d is the ambient level (either 1.9 or 254.6 ug/m^3); values (8/24) and (240/365) reflect that a worker worked 8 hours per day, 240 days for a year; and the factor (ℓ/L) represents the ratio of time in years an "average" worker was exposed and the average age of the cohort when the study terminated. In the absence of detailed information, the ratio (ℓ/L) is assumed to be 1/4, as usually estimated in other cohort studies.

The carcinogenic potency of hexavalent chromium (Cr VI) is calculated to range from

$$B = (8.5-1) \times 0.036/14.0 = 1.9 \times 10^{-2}/ug/m^3$$

to

$$B = (8.5-1) \times 0.036/0.1 = 2.7/\text{ug/m}^3.$$

The geometric mean of these two limits is $0.23/\text{ug/m}^3$. It is noted that even the lower range of the estimate ($1.9 \times 10^{-2}/\text{ug/m}^3$) is greater than the potency estimate calculated from the Mancuso (1975) data ($1.2 \times 10^{-2}/\text{ug/m}^3$).

7.2.3.3. POTENCY ESTIMATION BASED ON AXELSSON ET AL. (1980) -- The study cohort consisted of 1,876 men who were employed for one or more years between 1930 and 1975 and who were alive as of 1951. The chromium-exposed population was compared with males in the county in which the plant was located. The workers were classified into four groups consisting of (1) arc-furnace workers; (2) workers in transport, metal grinding, and sampling; (3) maintenance workers; and (4) office workers. The study did not show a significant increase of respiratory cancer in the exposed population, except in the case of the maintenance workers. Four respiratory cancers were observed in the group of 315 maintenance workers versus one expected. Of the four cases of respiratory cancer, two were diagnosed as mesotheliomas which the authors suggested may have resulted from exposure to asbestos. Excluding the two cases of mesotheliomas, the relative risk for lung cancer is 2, which is not statistically significant. To utilize the data from a negative study, the 95% upper limit of the relative risk, 3.7, is used to calculate an upper-bound estimate of potency.

The ambient levels of hexavalent chromium to which the maintenance workers were exposed was estimated to be 50 ug/m^3. The authors cautioned against the use of this exposure estimate. However, the authors did not indicate how the estimate was obtained and did not provide hints as to whether this estimate is likely to be higher or lower than the true ambient levels.

Using the relative risk of 3.7 and the ambient level of 50 ug/m^3, the carcinogenic potency of hexavalent chromium is estimated to be

$$B = (3.7 - 1) \times 0.036/2.7 = 3.5 \times 10^{-2}/ug/m^3$$

where the lifetime dose 2.7 ug/m^3 is calculated by

$$50 \times (8/24) \times (240/365) \times (1/4) = 2.7\ ug/m^3.$$

7.2.3.4. POTENCY ESTIMATION BASED ON POKROVSKAYA ET AL. (1973) -- Although this study showed a significant increase of lung cancer mortality over the control group, the validity of the data is questionable because the study cohort is not clearly defined. The report indicates that the cancer mortalities over the period 1955-1969 in workers from a ferroalloy plant in the Soviet Union were compared with the population of similar ages in the city where the plant was located, but it fails to indicate the criteria by which workers were included in the cohort. The lung cancer mortaiity ratios were reported to be 4.4 for the age group 30-39 and 6.6 for the age group 50-59 among male workers. Concentrations of hexavalent chromium were reported to exceed the marginally allowable value (0.01 mg/m^3) by 2 to 7 times on the average. The length of employment was from 7 to 20 years, with an average of 15 years.

Based on the information that the average ambient concentrations of hexavalent chromium exceeded the marginally allowable value 0.01 mg/m^3 by 2 to 7 times, workers' exposure to hexavalent chromium ranged from 0.02 mg/m^3 to 0.07 mg/m^3. The lifetime doses corresponding to 0.02 mg/m^3 and 0.07 mg/m^3 are, respectively, as follows:

$$d_1 = 0.02 \times 10^3 \times (8/24) \times (240/365) \times (1/4) = 1.1\ ug/m^3$$

and

$$d_2 = 0.07 \times 10^3 \times (8/24) \times (240/365) \times (1/4) = 3.8 \text{ ug/m}^3$$

If 6.6 is taken to be an estimate of the average relative risk for the cohort, then the carcinogenic potency for hexavalent chromium (Cr VI) is calculated to range from

$$B = (6.6-1) \times 0.036/3.8 = 5.2 \times 10^{-2}/\text{ug/m}^3$$

to

$$B = (6.6-1) \times 0.036/1.1 = 0.18/\text{ug/m}^3$$

The geometric mean of the two limits is 9.7×10^{-2}/ug/m^3. It is about 8 times larger than 1.2×10^{-2}/ug/m^3, the potency calculated on the basis of the Mancuso (1975) data.

7.2.3.5. COMPARISON OF UNIT RISK ESTIMATES ON THE BASIS OF DIFFERENT HUMAN STUDIES -- The carcinogenic potency, B, calculated on the basis of data from the three foreign studies cited above, can be used to calculate unit risks by means of the formula $P(d) = 1-\exp(-B \times d)$ with $d = 1$ ug/m^3. When $B \times d$ is small, $P(d)$ can be approximated by $B \times d$. The results of these calculations, along with the unit risk estimate of Mancuso (1975), are presented in Table 7-20. Lower, best, and upper limits are provided. These limits reflect various uncertainties associated with the calculation of potency estimates. For the Mancuso study, the lower limit represents the uncertainties associated with possible underestimation of the chromium exposure levels and the smoking habits of the cohort workers. It is assumed that the risk calculated without correcting these factors is overestimated by four times. The upper limit for the Mancuso study is calculated by assuming that the ratio of trivalent chromium (Cr III) and hexavalent chromium (Cr VI) is 6, and thus the risk is underestimated by seven times. For Langard et al. (1980) and Pokrovskaya et al. (1980), the "best" estimate is the geometric mean of the lower and upper limits, which correspond, respectively, to the maximum and minimum hexavalent chromium ambient levels reported. For Axelsson et al., the statistical upper limit (95% confidence limit) is used as the best and upper-limit estimate because the study was negative.

TABLE 7-20. COMPARISON OF UNIT RISKS (LIFETIME RISK DUE TO 1 ug/m^3 OF HEXAVALENT CHROMIUM IN AIR)

Data base	Lower limit	Best estimate	Upper limit
Mancuso (1975)	3.0×10^{-3}	1.2×10^{-2}	8.4×10^{-2}
Langard et al. (1980)	1.9×10^{-2}	1.3×10^{-1}	9.3×10^{-1}
Axelsson et al. (1980)	Not available	3.5×10^{-2}	3.5×10^{-2}
Pokrovskaya et al. (1973)	5.2×10^{-2}	9.2×10^{-2}	1.6×10^{-1}

7.2.3.6. RELATIVE CARCINOGENIC POTENCY OF CHROMIUM -- Figure 7.1 is a histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the CAG. Table 7-21 presents the potency index for these 53 suspect carcinogens. The potency index for a compound is a rounded-off number expressed in terms of (mMol/kg/day)$^{-1}$. Where human data are available for an agent, they have been used to calculate the index. Where no human data are available, animal oral studies have been used in preference to animal inhalation studies.

Based on the occupational study by Mancuso (1975) and the assumption that the daily air intake of a 70-kg man is 20 m^3, the potency index for chromium is calculated as $4 \times 10^{+3}$, which lies in the first quartile of the distribution.

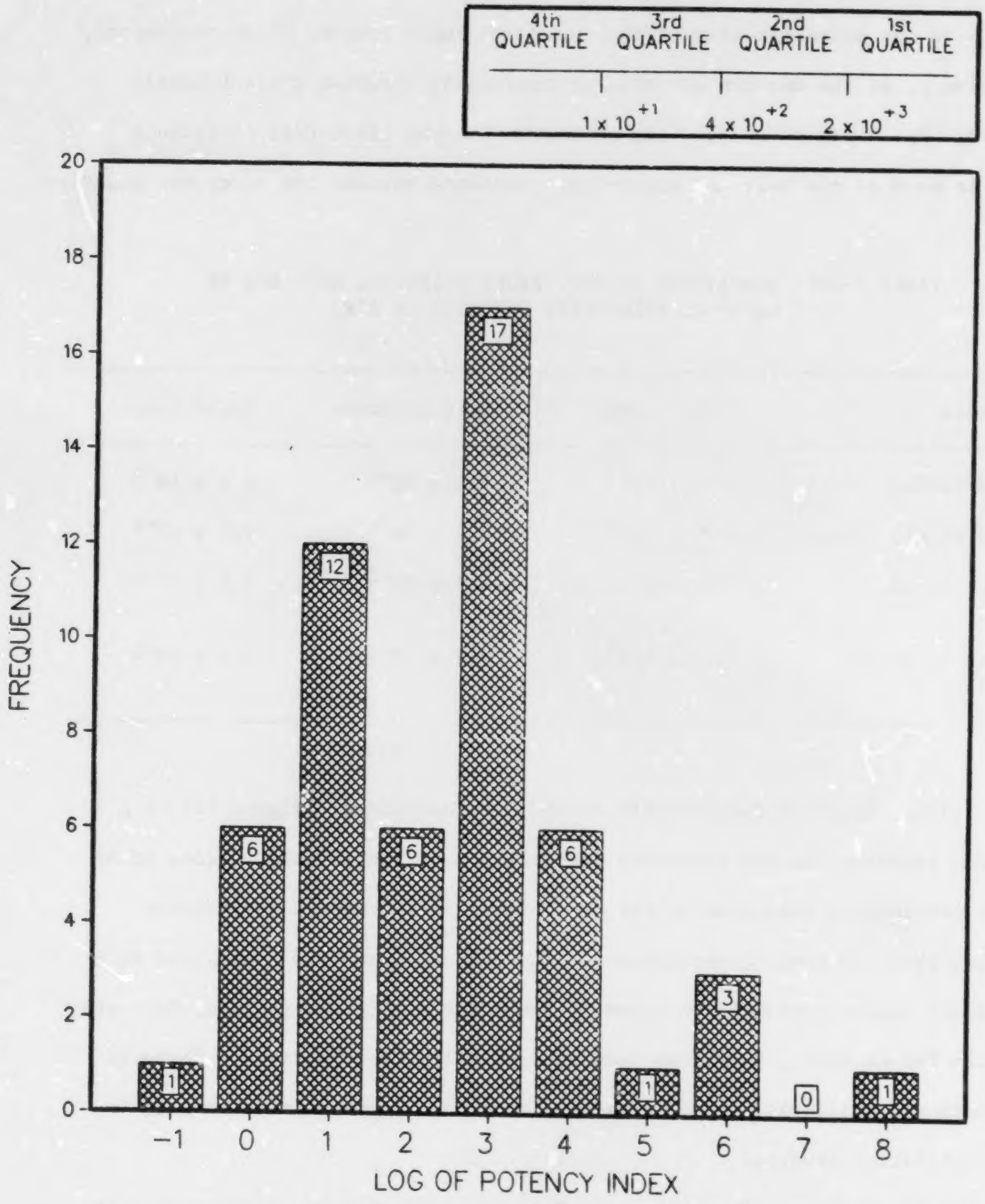

Figure 7-1. Histogram representing the frequency distribution of the potency indices of 53 suspect carcinogens evaluated by the Carcinogen Assessment Group.

TABLE 7-21. RELATIVE CARCINOGENIC POTENCIES AMONG 53 CHEMICALS EVALUATED BY THE CARCINOGEN ASSESSMENT GROUP AS SUSPECT HUMAN CARCINOGENS[1,2,3]

Compounds	Slope (mg/kg/day)$^{-1}$	Molecular weight	Potency index	Order of magnitude (log^{10} index)
Acrylonitrile	0.24(W)	53.1	$1x10^{+1}$	+1
Aflatoxin B_1	2924	312.3	$9x10^{+5}$	+6
Aldrin	11.4	369.4	$4x10^{+3}$	+4
Allyl chloride	$1.19x10^{-2}$	76.5	$9x10^{-1}$	0
Arsenic	15(H)	149.8	$2x10^{+3}$	+3
B[a]P	11.5	252.3	$3x10^{+3}$	+3
Benzene	$5.2x10^{-2}$(W)	78	$4x10^{0}$	+1
Benzidene	234(W)	184.2	$4x10^{+4}$	+5
Beryllium	1.40(W)	9	$1x10^{+1}$	+1
Cadmium	7.8(W)	112.4	$9x10^{+2}$	+3
Carbon tetrachloride	$1.30x10^{-1}$	153.8	$2x10^{+1}$	+1
Chlordane	1.61	409.8	$7x10^{+2}$	+3
Chlorinated ethanes				
1,2-dichloroethane	$6.9x10^{-2}$	98.9	$7x10^{0}$	+1
hexachloroethane	$1.42x10^{-2}$	236.7	$3x10^{0}$	0
1,1,2,2-tetrachloroethane	0.20	167.9	$3x10^{+1}$	+1
1,1,2-trichloroethane	$5.73x10^{-2}$	133.4	$8x10^{0}$	+1
Chloroform	$7x10^{-2}$	119.4	$8x10^{0}$	+1
Chromium	41(W)	100	$4x10^{+3}$	+4
DDT	8.42	354.5	$3x10^{+3}$	+3
Dichlorobenzidine	1.69	253.1	$4x10^{+2}$	+3
1,1-dichloroethylene	$1.47x10^{-1}$(I)	97	$1x10^{+1}$	+1
Dieldrin	30.4	380.9	$1x10^{+4}$	+4

(continued on the following page)

TABLE 7-21. (continued)

Compounds	Slope (mg/kg/day)$_{-1}$	Molecular weight	Potency index	Order of magnitude (log$_{10}$ index)
2,4-Dinitrotoluene	0.31	182	6x10^{+1}	+2
Diphenylhydrazine	0.77	180	1x10^{+2}	+2
Epichlorohydrin	9.9x10^{-3}	92.5	9x10^{-1}	0
Bis(2-chloroethyl)ether	1.14	143	2x10^{+2}	+2
Bis(chloromethyl)ether	9300(I)	115	1x10^{+6}	+6
Ethylene dibromide (EDB)	8.51	187.9	2x10^{+3}	+3
Ethylene oxide	1.26(I)	44.1	6x10^{+1}	+2
Heptachlor	3.37	373.3	1x10^{+3}	+3
Hexachlorobenzene	1.67	284.4	5x10^{+2}	+3
Hexachlorobutadiene	7.75x10^{-2}	261	2x10^{+1}	+1
Hexachlorocyclohexane				
technical grade	4.75	290.9	1x10^{+3}	+3
alpha isomer	11.12	290.9	3x10^{+3}	+3
beta isomer	1.84	290.9	5x10^{+2}	+3
gamma isomer	1.33	290.9	4x10^{+2}	+3
Hexachlorodibenzodioxin	6.2x10^{+3}	391	2x10^{+6}	+6
Methylene chloride	6.3x10^{-4}	84.9	5x10^{-2}	-1
Nickel	1.15(W)	58.7	7x10^{+1}	+2
Nitrosamines				
Dimethylnitrosamine	25.9(not by q_1^*)	74.1	2x10^{+3}	+3
Diethylnitrosamine	43.5(not by q_1^*)	102.1	4x10^{+3}	+4
Dibutylnitrosamine	5.43	158.2	9x10^{+2}	+3
N-nitrosopyrrolidine	2.13	100.2	2x10^{+2}	+2
N-nitroso-N-ethylurea	32.9	117.1	4x10^{+3}	+4
N-nitroso-N-methylurea	302.6	103.1	3x10^{+4}	+4
N-nitroso-diphenylamine	4.92x10^{-3}	198	1x10^{0}	0

(continued on the following page)

TABLE 7-21. (continued)

Compounds	Slope (mg/kg/day)$_{-1}$	Molecular weight	Potency index	Order of magnitude (log$_{10}$ index)
PCBs	4.34	324	$1x10^{+3}$	+3
Phenols				
2,4,6-trichlorophenol	$1.99x10^{-2}$	197.4	$4x10^{0}$	+1
Tetrachlorodibenzo-p-dioxin	$1.56x10^{+5}$	322	$5x10^{+7}$	+8
Tetrachloroethylene	$3.5x10^{-2}$	165.8	$6x10^{0}$	+1
Toxaphene	1.13	414	$5x10^{+2}$	+3
Trichloroethylene	$1.9x10^{-2}$	131.4	$2.5x10^{0}$	0
Vinyl chloride	$1.75x10^{-2}$(I)	62.5	$1x10^{0}$	0

Remarks:

1. Animal slopes are 95% upper-limit slopes based on the linearized multistage model. They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure). Human slopes are point estimates based on the linear non-threshold model.

2. The potency index is a rounded-off slope in $(mMol/kg/day)^{-1}$ and is calculated by multiplying the slopes in $(mg/kg/day)^{-1}$ by the molecular weight of the compound.

3. Not all of the carcinogenic potencies presented in this table represent the same degree of certainty. All are subject to change as new evidence becomes available.

This provides an estimate of the relative potency of chromium in comparison with other suspect carcinogens evaluated by the CAG.

7.2.4. Summary. Epidemiologic studies of chromate production facilities in the United States, Great Britain, West Germany, and Japan have all found an association between occupational exposure to chromium and lung cancer. Workers in the chromate production industry are exposed to both trivalent chromium (Cr III) and hexavalent chromium (Cr VI) compounds. Most of the epidemiologic studies did not attempt to determine which chromium compounds were the etiologic agents.

The strength of the association of exposure in the chromate production industry with lung cancer is evident by the high lung cancer mortality ratios found in various studies, the consistency of results by different investigators in different countries, the dose-response found in several studies, and the specificity of the tumor site (i.e., the lung). The respiratory cancer mortality ratio for chromate production workers was found to be as high as 29 by Brinton et al. (1952) and as low as 2.0 by Korallus et al. (1982). Comparison of mortality ratios across studies would not be valid because of differences in exposure intensity and duration, length of observation period, and percentages of the cohort lost to follow-up. Certainly, however, the magnitude of the mortality ratios found in several studies (studies of three independent cohorts of chromate production workers found lung cancer mortality ratios of at least 9.5 or greater) lends strong support to the association of exposure in the chromate production industry with lung cancer.

Three studies of the chrome pigment industry, one in Norway, one in Great Britain, and the third in the Netherlands and Germany, have also found an association between occupational exposure to chromium and lung cancer. The predominant chromium exposure in the chrome pigment industry is to hexavalent chromium (Cr VI). One study of the chromium plating industry in England (Royle 1975) reported that workers exposed primarily to hexavalent chromium (chromic acid mist and some dichromate dust) had significantly ($P < 0.05$) higher mortality from cancer at all sites than the control group; respiratory cancer mortality was not found to be elevated, however, and the follow-up period was only for 3 years. Thus, the results are inconclusive. The results of a Japanese study of chrome platers (Okubo and Tsuchiya 1979) were negative. A proportionate mortality study by Silverstein et al. (1981) of a die-casting and electroplating plant where chromium was used for electroplating found an excess of lung cancer mortality, but because of the presence of other carcinogens in the plant, no conclusions regarding the association of chromium and lung cancer can be drawn from this particular study. The results of studies of the ferrochromium industry are inconclusive as to lung cancer risk.

In most of the studies, smoking data were inadequate for any detailed analyses of smoking as a confounding variable with respect to lung cancer. However, the relative risks of lung cancer found by several of the studies of chromate production workers were higher than the risks that would be expected on the basis of differences in smoking habits between the study group and the controls. Also, the dose-response in terms of length of time worked in the industry seen in the Hayes et al. (1979) and the Taylor (1966) studies, and the dose-response found by Mancuso (1975), in terms of mg/m^3-years of total chromium, are not likely to be explained by differences in smoking habits among the dose groups.

Using the International Agency for Research on Cancer (IARC) classification scheme for the assessment of human evidence of carcinogenicity, the CAG considers that the epidemiologic evidence of the carcinogenicity of chromium is sufficient to establish a causal relationship between chromium and cancer in humans.

Chromium compounds have not induced significantly increased incidences of tumors in laboratory animals following exposure by the inhalation and ingestion routes. Neither trivalent (Cr III) nor hexavalent (Cr VI) chromium compounds have induced significantly increased incidences of lung tumors by inhalation. Similar results have been obtained following the ingestion of trivalent chromium compounds; however, these studies have not been reported in detail. There is some positive evidence that hexavalent chromium compounds are carcinogenic following subcutaneous injection or intrabronchial, intrapleural, intramuscular, or intratracheal implantation; however, implantation site tumors have only consistently been demonstrated using intramuscular implantation. Of all the chromium salts, calcium chromate is the only one that has been consistently shown to be carcinogenic in rats by several routes. Other chromium compounds, strontium chromate, zinc chromate, sodium dichromate, lead chromate, lead chromate oxide, and sintered chromium trioxide, have produced local sarcomas or lung tumors in rats at the site of application. Although the studies available indicate that metallic chromium powder and trivalent chromium compounds are not carcinogenic, these compounds have been studied less extensively than hexavalent chromium compounds. The relevance of studies using intramuscular implantation to human risk following inhalation or oral exposure to chromium compounds is not clear; however, these animal studies suggest that some hexavalent chromium compounds are likely to be the etiologic agent in human chromium-related cancer.

Although a number of epidemiologic studies have found an association between exposure to chromium compounds and lung cancer, the best data that can be used for estimating cancer risks due to exposure to chromium compounds are found in the study by Mancuso (1975). Mancuso (1975) reported age-specific lung cancer mortality data for chromate production workers in terms of total chromium exposure, which included exposure to both trivalent (Cr III) and hexavalent (Cr VI) chromium compounds. As noted previously, available data suggest that only hexavalent chromium compounds are carcinogenic.

Thus, a cancer risk estimate based on total chromium exposure will underestimate the risk due to hexavalent chromium alone. In the Bourne and Yee (1950) study, the ratio of trivalent (Cr III) to hexavalent (Cr VI) chromium in the airborne dust in the plant's nine major departments ranged from 1 to 3, except in the case of two departments, where the ratios were 6 for the lime and ash operation and as high as 52 for the ore preparation operation. Therefore, the ratio of trivalent and hexavalent chromium in the plant did not exceed 52, seems unlikely to exceed 6, and may be smaller. Thus, the underestimation of the risk from hexavalent chromium when the Mancuso (1975) data on exposures to total chromium are used is unlikely to be more than sevenfold, if the ratio is assumed to be 6. There are two other factors, however, that may result in an overestimation of the risk: (1) there is a possibility that the use of 1949 hygiene data may result in some degree of underestimation of worker's exposures, and (2) the risk presented in this report may be somewhat overestimated because of the implicit assumption that the smoking habits of chromate workers were similar to those of the general white male population. It is difficult to determine how much the risk has been overestimated in this regard. However, it seems reasonable to assume that the risk is not overestimated by more than 4 times on the assumption that 80% of the chromium workers and 50% of the control population smoked cigarettes, and that the exposure may be underestimated by a factor of 2.

Thus, these factors must be considered when interpreting the CAG's approximation, calculated from the Mancuso (1975) data, of the lifetime cancer risk due to a constant exposure to air containing 1 ug/m^3 of hexavalent chromium

(Cr VI). The unit risk is calculated as 1.2×10^{-2} on the basis of total chromium in the chromate plant. As discussed previously, this figure could either underestimate or overestimate the risk of hexavalent chromium. The use of total chromium as a surrogate for hexavalent chromium could result in an underestimate of the risk from hexavalent chromium by no more than 7 times; on the other hand, underestimation of plant exposures and of smoking habits in the workers could lead to an overestimate of the risk by roughly 4 times. On balance, the estimate based on the Mancuso data is judged to be the best possible estimate of the risk from hexavalent chromium.

Data from three studies on ferrochromium plants in Norway, Sweden, and the Soviet Union have also been used to calculate the carcinogenic potency of hexavalent chromium (Cr VI). Each of these studies has at least one characteristic (e.g., underestimation of ambient chromium concentration, concurrent exposure to asbestos, and ill-defined cohort) that makes it less adequate than the Mancuso study for purposes of risk assessment. Most of these characteristics tend to overestimate the risk. The deficiences of these foreign studies are addressed in detail in the epidemiology section. As may be expected, the carcinogenic potency (and hence, the unit risk) estimated from the Mancuso data is consistently smaller (but within a factor of 5) than the lower-limit potency estimates calculated from the three foreign studies.

7.2.5. Conclusions. The following conclusions can be made:

1. Using the IARC criteria, the epidemiologic studies of chromate production workers would be classified as sufficient evidence of carcinogenicity.
2. Using the IARC criteria, the evidence of the carcinogenicity of hexavalent chromium (Cr VI) in animal bioassay studies would be considered sufficient. The results in animals appear to be determined to some extent by the solubility of hexavalent chromium compounds. Trivalent chromium (Cr III)

has not yet been found to be carcinogenic in animal studies.

3. Accepting the findings as reported elsewhere in this document, hexavalent chromium (Cr VI) is mutagenic. The CAG considers this to be supportive of the finding that hexavalent chromium is carcinogenic in animal bioassays.

The lifetime cancer risk due to air containing 1 ug/m^3 of hexavalent chromium compounds is estimated to be 1.2×10^{-2}. This would place hexavalent chromium (Cr VI) in the first quartile of the 53 compounds evaluated by the CAG for relative carcinogenic potency.

Using the IARC classification scheme, the level of evidence available for the combined animal and human data would place hexavalent chromium (Cr VI) compounds into Group 1, meaning that there is decisive evidence for the carcinogenicity of those compounds in humans.

7.3. GENOTOXICITY

7.3.1. In Vitro Mutagenicity. In an attempt to understand the fundamental biological activity of metals and its relationship to carcinogenesis, numerous in vitro experiments have been conducted. Many of these studies attempt to exploit the strong relationships between molecular events involved in mutagenesis and carcinogenesis. In particular, the interaction of xenobiotics with nucleic acids is believed to be a critical event in mutagenesis and/or cell transformation. Cultures of mammalian cells and bacteria, as well as cell-free systems, have been used to explore the potential mutagenicity/carcinogenicity of chromium salts. Although mutagenicity assays employing bacterial tester strains have received widespread use in screening compounds for mutagenicity (e.g., Ames assay), these assay systems have not been frequently employed for screening metals. Nevertheless, positive results have been obtained with several metals in both in vitro mutagenicity assays and assays using DNA repair deficient bacteria. A summary of the results obtained from in vitro mutagenicity assays of chromium compounds are presented in Table 7-22.

In an early study of the mutagenicity of chromium in bacteria, Venitt and Levy (1974) tested three soluble Cr(VI) salts (Na_2CrO_4, K_2CrO_4, and $CaCrO_4$) for mutagenic activity using a spot test. Following application of each compound to the plate at levels of 0.05, 0.10, or 0.20 μmol, a 3-fold increase was observed in the number of reversion colonies in the tester organism E. coli WP2 (try^-). Similar results were observed with both E. coli WP2 and WP2 uvrA (absence of excision-repair) were exposed to Na_2CrO_4 in suspension, followed by removal of the test compound and plating on minimal plates. Repair deficient E. coli WP2 (exrA, error prone DNA repair) and WP2 uvrA were compared with wild type E. coli WP2 for mutagenic response in the spot test to K_2CrO_4. Since all tester

TABLE 7-22

The *In Vitro* Mutagenicity Bioassay of Chromic Compounds

Test	Indicator Organism	Compound Tested	Valence State	Metabolic Activation	Dose	Application	Response	Reference
Reverse mutation	*E. coli* WP2 (try$^-$)	Na_2CrO_4	+6	no	0.05, 0.10, and 0.20 µmol/plate	spot test	+	Venitt and Levy, 1974
		K_2CrO_4	+6	no			+	
		$CaCrO_4$	+6	no			+	
Reverse mutation	*E. coli* WP2 (try$^-$)	Na_2CrO_4	+6	no	0.5 to 5 mg/mℓ	suspension assay	+	Venitt and Levy, 1974
	E. coli WP2 uvrA	Na_2CrO_4	+6	no	0.5 to 5 mg/mℓ	suspension assay	+	
Reverse mutation	*E. coli* WP2 (try$^-$)	K_2CrO_4	+6	no	0.05 µmol/plate	spot test	+	Venitt and Levy, 1974
	E. coli WP2 uvrA	K_2CrO_4	+6	no	0.05 µmol/plate	spot test	+	
	E. coli WP2 exrA	K_2CrO_4	+6	no	0.05 µmol/plate	spot test	+	
Reverse mutation	*E. coli* WP2	$K_2Cr_2O_7$	+6	no	4.0×10^{-3}M	suspension assay	+	Nishioka, 1975
	E. coli WP2 uvrA	$K_2Cr_2O_7$	+6	no	1.2×10^{-3}M	suspension assay	+	
	E. coli CM571	$K_2Cr_2O_7$	+6	no	1.2×10^{-3}M	suspension assay	-	
Reverse mutation	*E. coli* Hs30R	$K_2Cr_2O_4$	+6	no	13.0×10^{-3}M	suspension assay	+*	Nakamuro et al., 1978
		$K_2Cr_2O_7$	+6	no	13.0×10^{-3}M	suspension assay	+*	
Reverse mutation	*E. coli* WP2	K_2CrO_4	+6	no	0.5 µg/mℓ	fluctuation test	+	Green et al., 1976
Reverse mutation	*E. coli* WP2	$K_2Cr_2O_7$	+6	no	NR	spot test	+	Kanematsu et al., 1980
	E. coli B/r WP2	$K_2Cr_2O_7$	+6	no	NR	spot test	-	
Reverse mutation	*S. typhimurium* TA92	chromate*	+6	no	NR	plate incorporation	+	Lofroth and Ames, 1978
		dichromate*	+6	no	NR	plate incorporation	+	
Reverse mutation	*S. typhimurium* TA1978, TA92	chromate*	+6	no	100 and 200 nmol/plate	plate incorporation	+	Lofroth, 1978
		dichromate*	+6	no	100 and 200 nmol/plate	plate incorporation	+	
		chromate*	+6	yes	100 and 200 nmol/plate	plate incorporation	-	
		dichromate*	+6	yes	100 and 200 nmol/plate	plate incorporation	-	

TABLE 7-22 (cont.)

Test	Indicator Organism	Compound Tested	Valence State	Metabolic Activation	Dose	Application	Response	Reference
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA100, TA98	$K_2Cr_2O_7$	+6	no	NR	spot test	-	Kanematsu et al., 1980
Reverse mutation	*S. typhimurium*	$Na_2Cr_2O_7$	+6	no	10 to 40 μg/plate	plate incorporation	+	DeFlora, 1978; Petrilli and DeFlora, 1978
		$Na_2Cr_2O_7$	+6	yes	10 to 80 μg/plate	plate incorporation	-	
Reverse mutation	*S. typhimurium* TA1535, TA1537 TA98, TA100	$Na_2Cr_2O_7$	+6	no	10 to 200 μg/plate	plate incorporation	+	Petrelli and DeFlora, 1977, 1978
		CrO_3	+6	no	10 to 200 μg/plate	plate incorporation	+	
		$CaCrO_4$	+6	no	10 to 200 μg/plate	plate incorporation	+	
		$K_2Cr_2O_7$	+6	no	10 to 200 μg/plate	plate incorporation	+	
		$ZnCrO_4 \cdot Zn(OH)_2$	+6	no	10 to 200 μg/plate	plate incorporation	+	
		$Na_2Cr_2O_7$	+6	yes	10 to 200 μg/plate	plate incorporation	-	
		CrO_3	+6	yes	10 to 200 μg/plate	plate incorporation	-	
		$CaCrO_4$	+6	yes	10 to 200 μg/plate	plate incorporation	-	
		$K_2Cr_2O_7$	+6	yes	10 to 200 μg/plate	plate incorporation	-	
		$ZnCrO_4 \cdot Zn(OH)_2$	+6	yes	10 to 200 μg/plate	plate incorporation	-	
Forward mutation	*Schizosaccharomyces pombe*	$K_2Cr_2O_7$	+6	no	10^2 μM	suspension	+*	Bonatti et al., 1976
Forward mutation to 8-azaguanine resistance	Chinese Hamster V79 cells	$K_2Cr_2O_7$	+6	no	0.35 to 0.78 μg/mℓ	in culture medium	+	Newbold et al., 1979
		$ZnCrO_4$	+6	no	1 to 4 μg/mℓ	in culture medium	+	
		$PbCrO_4$	+6	no	5 to 10 μg/mℓ	in culture medium	-	

TABLE 7-22 (cont.)

Test	Indicator Organism	Compound Tested	Valence State	Metabolic Activation	Dose	Application	Response	Reference
Gene conversion	*Schizosaccharomyces pombe*	$K_2Cr_2O_7$	+6	no	10^2 to 10^5 μM	suspension	+	Bonatti et al., 1976
Gene conversion	*Saccharemyces cerevisiae* D7	CrO_3	+6	no	10^{-2} to 10^{-3}	suspension	+	Fukunaga et al., 1982
Reverse mutation	*E. coli* (try^-)	$Cr_2(SO_4)_3K_2SO_4 \cdot 24H_2O$	+3	no	NR	spot test*	-	Venitt and Levy, 1974
Reverse mutation	*E. coli* H_530R	$Cr(CH_3COO)_3$	+3	no	130 x 10^{-3}M	suspension assay	+*	Nakamuro et al., 1978
Reverse mutation	*S. typhimurium* TA98, TA1537, TA1535, TA100	$CrK(SO_4)_2 \cdot 12H_2O$	+3	no/yes	20 mg/plate	plate incorporation	-	Petrilli and DeFlora, 1977
		$CrCl_3 \cdot 6H_2O$	+3	no/yes		plate incorporation	-	
Reverse mutation	*S. typhimurium* TA100	$CrK(SO_4)_2 \cdot 12H_2O$	+3	no/yes	800 μg/plate	plate incorporation	-	Petrilli and DeFlora, 1978a,b
		$CrCl_3 \cdot 6H_2O$	+3	no			-	
		$Cr(NO_3)_3 \cdot 9H_2O$	+3	no			-	

* = Refer to text for further information.

NR = Not reported

organisms yielded approximately the same mutagenic response regardless of the presence or absence of DNA repair pathways, the authors concluded that chromium directly interacted with DNA, with subsequent mispairing of bases occurring during cell division. Other possible explanations for these results were not considered. The soluble Cr(III) compound, $Cr_2SO_4K_2SO_4 \cdot 2H_2O$ [This was the formula given in the report, although the test compound was probably $Cr_2(SO_4)_3 \cdot K_2SO_4 \cdot 24H_2O$.], gave negative results (specifics in experimental protocol were not given), along with soluble salts of tungsten, molybdenum, zinc, cadmium, and mercury.

Nishioka (1975) obtained positive mutagenic results with $K_2Cr_2O_7$(VI) in a suspension assay using the tester strain E. coli WP2 and WP2 uvrA, but not in the tester strain E. coli CM_{571}. Since strain CM_{571} is a recombination-deficient strain, it was postulated that metal mutagenesis needed some component of the recA allele. Positive results were also reported for $K_2Cr_2O_7$ by Kanematsu et al. (1980) in the spot test using strain E. coli WP2; however, E. coli B/r WP2 was negative (no dose information was presented in this study). Nakamuro et al. (1978) used E. coli Hs30R, a uvrA minus mutant requiring arginine, to study the mutagenicity of $K_2Cr_2O_7$(VI) and K_2CrO_4(VI), and $Cr(CH_3COO)_3$(III) in a suspension assay. The respective mutagenic frequency of these compounds was 134, 45, and 30 mutants x 10^8 viable cells. Although positive mutagenic responses were reported for all test substances, the low survival of between 4 and 10% at the doses which were reported as mutagenic may lead to artifacts, particularly if spontaneous revertants arise during growth on the trace levels of arginine used to supplement the top agar, as suggested by Green (1976).

Green et al. (1976) also observed mutation in E. coli WP2 using a fluctuation test. At levels of 0.5 μg/mℓ K_2CrO_4, 148 of 250 tubes were positive as compared to 64 in controls. At a high dose of 2.5 μg/mℓ, only 10 of 150 tubes were positive as compared with 34 tubes in the controls. The apparent anti-mutagenic effect at the higher dose was attributed to the toxicity of the K_2CrO_4.

The mutagenicity of chromium compounds has been assessed in the Ames assay, which uses specially constructed histidine dependent strains of Salmonella typhimurium; however, in the original report on the validation of this assay, McCann et al. (1975) stated that the test was not suitable for metals as a result of the high concentration of magnesium, citrate, and phosphate salts in the media. Chromate and dichromate but not the chromic ion (the specific salt was not mentioned) were reported in an abstract to cause frameshift mutations in S. typhimurium strains containing the his D3052 and his C3076 mutations, as well as his G 46 strains containing the R factor. The greatest response was observed in TA92 with five revertants/nmol Cr. Kanematsu et al. (1980) has reported negative results with $K_2Cr_2O_7$ in the spot test using strains TA1535, TA100, TA98, TA1537, and TA1538; however, the lack of exposure information in this report makes it difficult to evaluate. In a recent study of the mutagenic activity of chromic chromate (18.5% Cr(VI), and 50% total chromium) in S. typhimurium strain TA1535, Witmer et al. (1982) reported that mutagenic activity, expressed as number of revertants on test plates ÷ number of revertants on spontaneous plates, was increased as the standard salt concentration of the minimal media was reduced. At least a portion of this observed increased activity resulted from the poor survival of the cells in the low salt media and the associated decrease in the number of spontaneous colonies. Although the author suggested that variation in the S. typhimurium assay may be useful in further evaluation of the mutagenic activity of inorganic compounds such as chromium, further validation of this method will be required before these results can be compared with the other available data on mutagenicity of chromium.

In further studies, Lofroth (1978) found that chromate and dichromate were mutagenic in strain TA1978 as well as TA92. On addition of a mammalian microsomal activation system (S-9 mix) prepared from the livers of Aroclor pretreated male rats, the number of revertants decreased from 206 and 357 (assays without activation system) to 89 and 89 (assays with activation system) for TA1978 and TA92, respectively. In the absence of NADP in the S-9 mix, the inhibition of chromium mutagenicity did not occur. It was also reported that addition of Cr(VI) to an aqueous solution of NADP did not change the valence state of chromium. It was concluded that NADP plus additional factors in the S-9 mix were necessary to inactivate Cr(VI), possibly by reduction to Cr(III). Similarly, Petrilli and DeFlora (1977) obtained positive responses with $Na_2Cr_2O_7$, CrO_3, $CaCrO_4$, and $K_2Cr_2O_4$ when assayed in strains TA1537, TA1535, TA98, and TA100 at levels between 10 and 200 μg/plate. When the response was expressed as revertants/μg of Cr(VI), there was no statistically significant difference in the activity of each of these compounds. The Cr(III) compounds, $CrK(SO_4)_2$ and $CrCl_3$, gave negative results.

DeFlora (1978) and Petrilli and DeFlora (1978a,b) further studied the effect of metabolic activation on the mutagenicity of Cr(VI) and (III). DeFlora (1978) observed a decrease in the mutagenicity of $Na_2Cr_2O_7$ in S. typhimurium strain TA100 in the presence of S-9 mix prepared from rat liver. When $Na_2Cr_2O_7$ was added at 40 μg/plate, the number of revertant colonies decreased from 705 to 420, 370, 283, 228, and 221 with the incorporation, respectively, of 0, 10, 20, 30, 40, and 50 μℓ of S-9 fraction/plate. Petrilli and DeFlora (1978b) extend these observations to the Cr(VI) compounds $Na_2Ca_2O_7$, CrO_3, K_2CrO_4, $ZnCrO_4 \cdot Zn(OH)_2$ (zinc yellow also contained 10% CrO_3), and $PbCrO_4 \cdot PbO$, with mutagenic activity in strains TA1535, TA1537, TA98, and TA100 detected in the absence of S-9 mix but not in the presence of S-9 mix, prepared from rat liver. Little or no loss of mutagenic activity occurred when the added S-9 was prepared from lung or muscle. Also, human plasma added to the top agar had no effect on chromium mutagenicity, but lysates of erythrocytes did result in the loss of mutagenic activity. The loss of mutagenicity was associated with reduction potential of components in the S-9 mix, with reduced GSH, TPNH, and G6PD plus S-9 mix (to generate TPNH) all inhibiting the mutagenicity of Cr(VI). In a study using varying levels of TPNH, the mutagenic response was correlated with the amount of $Na_2Cr_2O_7$ (originally 52 µg Cr(VI)/plate) that remained as Cr(VI). Conversely, Cr(III) as $CrK(SO_4)_2$, $CrCl_3$, and $Cr(NO_3)_3$, which were inactive in the Ames assay, were converted to active mutagens by the addition of nontoxic levels of the strong oxidizer $KMnO_4$ (Petrilli and DeFlora, 1978a). The presence of this oxidizing agent reversed the effect of S-9 mix on the mutagenicity of Cr(VI). These data supported the conclusions that the valence state of chromium was an important factor in producing a mutagenic response in the Ames assay, and that naturally occurring biological reducing agents were capable of reducing Cr(VI) to Cr(III). Although the studies show that Cr(VI) compounds produce a positive response, these studies do not indicate whether Cr(III) or (VI) is the ultimate mutagen which interacts with the DNA of the cell.

Further work on mutagenicity has also been reported by Warren et al. (1981), and De Flora (1981). Warren et al. tested 17 hexacoordinate Cr(III) compounds for DNA damage with the E. coli differential repair assay, and, for mutagenicity, with S. typhimurium. The compounds showed a parallel between mutagenicity and differential inhibition in the two bioassays. The greater the differential inhibition in the repair test, the more likely the compound was mutagenic. The genetically most active complexes were those that had a charge of +1 with two relatively stable ligands, along with four more stable aromatic amine ligands. The Cr(III) complexes were similar in size, reactivity and cellular transport to many ambient cellular molecules. They concluded that the reduction of Cr(VI) in the cell could result in a mutagenically active Cr(III) species.

De Flora (1981) tested 18 chromium compounds in the Salmonella microsome test designed to provide dose response curves and a potency rating. Ten of the eleven Cr(VI) compounds showed a mutagenic response, and the dose response range for the seven most reactive compounds was 1.4 to 5.1 net revertance per nmole. None of the pure Cr(III) compounds showed positive results. Chromite, which contained traces of Cr(VI), was positive only for a 2 mg spot test.

Petrilli and De Flora (1982) investigated whether the administration of dichromate in rats may modify the lung and S-9 fractions by decreasing Cr(VI) mutagenicity. They noted that daily intratracheal administration of sodium dichromate (0.25 mg/kg daily, 5 times/week for 4 weeks) increased Cr(VI) deactivation. On the other hand, S-9 fractions of muscle tissue had no effects on deactivation. From these preliminary results,they concluded that sub-chronic exposure to Cr(VI) could enhance the cytoplasmic defense mechanisms and thus raise the threshold of susceptibility.

Cr(VI) compounds have also been demonstrated to be mutagenic in vitro in eucaryotic test systems, while Cr(III) was inactive. Bonatti et al. (1976) exposed yeast, Schizosaccharomyces pombe, to 10^2 to 10^5 μM of $K_2Cr_2O_7$ in a forward mutation assay and a test for gene conversion. Forward mutation was observed in 7 of 480,054 colonies exposed to 10^2 μM $K_2Cr_2O_7$ for 7 hours, which was not statistically increased from controls in which no mutants were observed in 84,546 colonies; however, if comparison was made to the historical spontaneous mutation rate (no mutants in 10^6 colonies), then chromium significantly increased the mutation rate. In the study of gene conversion, there was a dose related increase in the four allelic combinations examined. The authors noted that there were limitations in this study, but that the data suggest that $K_2Cr_2O_7$ was mutagenic under the test conditions.

Using another strain of yeast, Saccharomyces cerivisiae D7, Fukanaga et al. (1982) examined the genetic activity of chromium trioxide. The compound was incubated with the cells at concentrations of 10^{-2} to 10^{-3} M for a period of 24 hours. Following incubation, the cells were plated to determine viability and recombination in the ade locus. The highest concentration tested caused nearly 100% cell death while viability at the lowest concentration was 77%. The crossover frequency in treated cells was dose dependent with the 10^{-2} M concentration resulting in a frequency of 1.4% as compared to 0.02% for untreated cells. It was also reported that only growing and not resting cells were susceptible to the effects of chromium, suggesting to the authors that chromium may affect the fidelity of DNA polymerase.

Forward mutagenesis to 8-azaguanine resistance in cultured Chinese hamster V79/4 cells was used by Newbold et al. (1979) to assess the genetic activity of both Cr(VI) and (III). The highly soluble and slightly soluble Cr(VI) salts, $K_2Cr_2O_7$ and $ZnCrO_4$, respectively, both produced dose related increases in 8-azaguanine resistant cell colonies, while the insoluble Cr(VI) compound, $PbCrO_4$, and the soluble Cr(III) compound, $Cr(CH_3COO)_3$, were inactive. The more soluble $K_2Cr_2O_7$ was ≈5-fold more active than the $ZnCrO_4$. It was stressed that both the valence state and solubility of a chromium compound affected its mutagenic potential. Although high solubility was necessary for a mutagenic response, the authors suggested that low solubility would facilitate a carcinogenic response, since compounds of lower solubility might remain in the body longer, providing a low dose continuous exposure to chromium.

7.3.2.. Effects On DNA And DNA Replication. It is apparent from the results of bioassays in both prokaryotic and eucaryotic systems that some chromium compounds are mutagenic. In general, soluble Cr(VI) compounds were positive in reverse and forward mutagenicity assays, while insoluble salts and Cr(III) compounds are inactive. Metabolic activation inhibited the mutagenicity of Cr(VI), probably by the reduction of the Cr(VI) to Cr(III) by cellular reducing agents such as GSH. Other studies have been performed which indicate that chromium compounds interact with DNA and decrease the fidelity of DNA polymerase, and this mechanism may participate in chromium induced mutagenesis.

The difference in the sensitivity of recombination deficient strains of bacteria as compared to wild type to the toxic effects of chromium compounds has been used as an indicator of DNA damage. Nishioka (1975) exposed both rec^- and rec^+ strains of Bacillus subtilis to $K_2Cr_2O_7$(VI), K_2CrO_4(VI), and $CrCl_3$(III) by placing 0.05 mℓ of 0.05 M solution on a filter disc placed on the agar surface. For the two Cr(VI) compounds, the zone of growth inhibition was greater for the rec^- strains as compared with the rec^+, indicating DNA damage, while there was no difference in the size of the zone of inhibition in the assay of $CrCl_3$. The positive rec-effect with $K_2Cr_2O_7$ was diminished sharply when the reducing agent, Na_2SO_3, was mixed with the test compound, indicating that the Cr(VI) oxidation state was necessary to cause DNA damage. Similarly, Kanematsu et al. (1980), in a survey of 127 metal compounds in the B. subtilis rec assay, reported that three Cr(VI) compounds (K_2CrO_4, $K_2Cr_2O_7$, and CrO_3) were positive at 0.05 mℓ of a 0.005 and 0.1 M solution, respectively, for the salts and oxide. Cr(III), $Cr_2(SO_4)_3$, was negative, and it was noted that the sample was toxic to the bacteria at the dose tested.

Nakamuro et al. (1978) examined three Cr(VI) compounds ($K_2Cr_2O_7$, K_2CrO_4, and CrO_3) and three Cr(III) compounds ($Cr(CH_3COO)_3$, $Cr(NO_3)_3$, and $CrCl_3$) in the rec^- assay with B. subtilis. The compounds were tested using 0.02 mℓ aliquots of solutions between 3.2×10^{-1} to 1.6×10^{-2} M for the Cr(VI) compound and 1.3 to 1.6×10^{-1} M for the Cr(III) compound. All compounds tested were positive except for $CrCl_3$(III). Although DNA damage as indicated by the rec effect was observed with two of the Cr(III) compounds, the order of activities was $K_2Cr_2O_7 > K_2CrO_4 > CrO_3 > Cr(CH_3OO)_3 > Cr(NO_3)_3$, with the Cr(VI) compounds being more active than the Cr(III) compounds.

In an attempt to determine the mechanism of DNA damage induced by chromium, Levis et al. (1978) examined the effects of $K_2Cr_2O_7$ exposure on DNA synthesis in cultured BHK cells. The cells were treated with 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} M $K_2Cr_2O_7$ for 1 to 4 hours, followed by determination of ^{3}H-thymidine uptake into DNA and the intracellular pools. At the two intermediate doses, increased specific activity was observed in both the nucleotide pool and DNA, which was attributed to chromium effects on the membrane transport of the exogenous labeled thymidine. When DNA synthesis was adjusted for the changes in the specific activity of the pools, transient and reversible inhibitions of DNA synthesis were observed at 10^{-6} M, and complete irreversible inhibition occurred at 10^{-5} M., It was reported that inhibition of DNA synthesis occurred prior to, and to a greater extent than, inhibition of protein or RNA synthesis. Although these effects on DNA synthesis may be partly related to the effects of chromium on the cellular membrane, Raffetto (1977) reported evidence of direct interaction with DNA in A18BcR cultured cells, as indicated by unscheduled DNA synthesis following treatment with $K_2Cr_2O_7$ (VI). In cells treated for 1 hour with 16, 4, or 1 μg Cr(III)/mℓ (as $CrCl_3$), no increase was produced. This evidence suggests that at least Cr(VI) can alter DNA synthesis by more than a single mechanism.

Loeb and coworkers (Sirova and Loeb, 1976; Loeb et al., 1977) have demonstrated that chromium compounds adversely affect the fidelity of DNA transcription. The compounds, $CrCl_3$ and CrO_3, were incubated with avian myeloblastosis virus DNA polymerase, a template with restricted base composition, and complementary deoxynucleoside radiolabeled with ^{32}P and noncomplementary deoxynucleoside labeled with ^3H. Following incubation, the error frequency was determined to be greater when either metal compound was added to the incubation system as compared to the controls. The error prone avian myeloblastosis virus DNA polymerase lacks exodeoxynuclease active for removal of noncomplementary base, thus providing optimum conditions for detecting the nonfidelity of DNA synthesis. In later studies, Tkeshelashvili et al. (1980) demonstrated a similar increase in misincorporation of complementary bases using synthetic polynucleotides and CrO_3 and $CrCl_3$ in an assay system containing E. coli DNA polymerase. Both compounds appeared to have approximately the same activity. Nearest neighbor analysis indicated that the noncomplementary bases were incorporated as single base substitution. Noncomplementary nucleotides were also incorporated with native DNA from bacteriophage $\Phi\chi174$ (am3) and E. coli DNA polymerase in vitro in the presence of CrO_3. Infidelity in DNA synthesis was detected by loss of an amber mutation which was assessed by growth of infected strains of E. coli nonpermissive and permissive for this mutation.

Tamino et al. (1981) examined the in vivo and in vitro binding of both Cr(VI) ($K_2Cr_2O_7$) and (III) ($CrCl_3$) to DNA from cultured BHK cell, and in vitro to commercial calf thymus DNA and synthetic polynucleotides. The interactions of Cr(III) with these nucleic acids in vitro was dependent on the G and C content, with synthetic poly(G) and poly(C) binding 1.05 chromium ions per 100 nucleotides. In vitro and in vivo reaction also changed the ultraviolet (UV) absorption spectra and thermal stability of the DNA. When Cr(VI) was used there was no observed change in the UV spectra whether exposure occurred in vitro or in vivo. The manner of treatment with Cr(VI) did affect the thermal stability of the DNA with in vitro exposure resulting in the same types of changes observed with Cr(III), while little change in thermal stability occurred with in vivo exposure to Cr(VI). The data indicate that Cr(III) has some capacity to cross biological membranes and interact with cellular DNA, and that the types of interactions between chromium and polynucleotides may be different for Cr(VI) and (III).

Although *in vitro* mutagenicity indicated that Cr(VI) compounds were generally active and Cr(III) compounds nonactive, the assays of chromium induced DNA damage in the rec assay, unscheduled DNA synthesis in mammalian cultured cells, and increased *in vitro* infidelity of DNA synthesis indicated that at least some activity is associated with both valence states (Nishioka, 1975; Nakamuro et al., 1978; Raffeto, 1977; Loeb et al., 1977; and Tkeshelashvili et al., 1980).

7.3.3. Chromium Induced Chromosomal Aberrations and Cell Transformations. *In vitro*, chromium has been shown to result in the appearance of chromosomal aberrations and cell transformation (Table 7-23). Fradkin et al. (1975) observed morphologic changes and loss of anchorage dependent growth in BHK21 cells treated with 0.25 and 0.5 μg of $CaCrO_4 \cdot 2H_2O$. Chromate transformed cells maintain the ability to grow independent of anchorage even after the cells were re-isolated and freed of exposure to $CaCrO_4 \cdot 2H_2O$. Tsuda and Kato (1977) observed morphologic transformation in primary hamster embryo cells after exposure to $K_2Cr_2O_7$(VI) at a level of 0.1, 0.2, and 0.5 μg/mℓ for 24 hours. The transformation frequency increased from 0.179% for the control cultures to 0.760, 2.86, and 2.70% for cells exposed to 0.1, 0.2, and 0.5 μg/mℓ, respectively. A transformation frequency of 2.10% was achieved with the positive control, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) at a level of 0.5 μg/mℓ. Conflicting results of exposure to $CrCl_3$(III) and $K_2Cr_2O_7$(VI) on morphologic transformation of BALB/c mouse fetus cells in culture was obtained in two experiments by Raffetto (1977). Although both experiments showed an increase in the number of transformed foci, this increase was not dose-related, and there was a 10-fold difference between the two experiments performed under similar conditions. The authors suggest

TABLE 7-23

Chromium Produced Clastogenic Effects and Cell Transformation

Test	Indicator Cells	Compound Tested	Valence State	Dose	Endpoint	Response	Reference
Cell transformation	BHK_{21}	$CaCrO_4 \cdot 2H_2O$	+6	0.25 and 0.5 µg/mℓ	Morphologic alterations, loss of anchorage dependent growth	+	Fradkin et al., 1975
Cell transformation	primary embryo hamster cells	$K_2Cr_2O_7$	+6	0.0, 0.1, 0.2, and 0.5 µg/mℓ	Morphologic alterations	Transformation frequency increased from 0.76% for controls to 2.70% for the high dose group	Tsuda and Kato, 1977
Cell transformation	BALB/c cells	$CrCl_3$ $K_2Cr_2O_7$	+3 +6	0.04 and 0.4 µg/mℓ 0.015 and 0.1 µg/mℓ	Morphologic alterations	+* +*	Raffetto, 1977
Cell transformation	primary embryo hamster cells	$CaCrO_4$ K_2CrO_4 $ZnCrO_4$	+6 +6 +6	0.006 mM 0.01 mM 0.01mM	Increased susceptibility to viral tranformation	2 x control levels 2 x control levels 4 x control levels	Casto et al., 1979
Host mediated cell transformation	primary embryo hamster cells	$NaCrO_4$	+6	2.5 µg/100g body weight on day 11 of gestation	Morphologic alteraations	+	DiPaolo and Casto, 1979
Clastogenic	BALB/c cells	$CrCl_3$ $K_2Cr_2O_7$	+3 +6	0.04 and 0.4 µg/mℓ 0.015 and 0.1 µg/mℓ	Chromosomal aberrations	+ at 0.4 µg/mℓ + at both doses	Raffetto, 1977
Clastogenic	CHO cells	$K_2Cr_2O_7$ $Na_2Cr_2O_7$ K_2CrO_4 Na_2CrO_4 CrO_3 $CaCrO_4$ $CrCl_3$ $Cr(NO_3)_3$ $KCr(SO_4)_2$ $Cr(COOCH_3)_3$	+6 +6 +6 +6 +6 +6 +3 +3 +3 +3	0.1 and 0.3 µg/mℓ 0.1 and 0.3 µg/mℓ 0.25 µg/mℓ 0.25 µg/mℓ 0.1 and 0.25 µg/mℓ 0.5 µg/mℓ 5 and 50 µg/mℓ 50 and 150 µg/mℓ 150 µg/mℓ 5 and 20 µg/mℓ	Chromosomal aberrations/100 cells (17 in control cultures)	36 and 56 58 and 169 42 41 and 65 60 and 62 102 21 and 31 15 and 21 32 38 and 39	Levis and Majone, 1979
Clastogenic	mouse FM3A cells	$K_2Cr_2O_7$ CrO_3 $Cr_2(SO_4)_3$	+6 +6 +3	3.2×10^{-7} to 3.2×10^{-6}M 1.0×10^{-6} to 1.0×10^{-5}M 3.2×10^{-5} to 1.0×10^{-3}M	Chromosomal aberrations	+ + -	Umeda and Nishimura, 1979
Clastogenic	hamster embryo cells	$K_2Cr_2O_7$	+6	0.5 µg/mℓ	Chromosomal aberrations	+*	Tsuda and Kato, 1977
Clastogenic	V79 cells	$K_2Cr_2O_7$	+6	0.35 to 0.8 µg/mℓ	Chromosomal aberrations	+	Newbold et al., 1979

TABLE 7-23 (cont.)

Test	Indicator Cells	Compound Tested	Valence State	Dose	Endpoint	Response	Reference
Clastogenic	cultured human leukocytes	$K_2Cr_2O_7$	+6	0.125 to 4.0×10^{-6} M	Chromosomal aberrations	+	Nakamuro et al., 1978
		K_2CrO_4	+6	0.5 to 8.0×10^{-6} M		+	
		$Cr(CH_3COO)_3$	+3	4 to 32 x 10^{-6} M		+ at $\geq 16 \times 10^{-6}$ M	
		$Cr(NO_3)_3$	+3	32.0 x 10^{-6} M		-	
		$CrCl_3$	+3	32.0 x 10^{-6} M		-	
Clastogenic	cultured human lymphocytes	$K_2Cr_2O_7$	+6	10^{-8} to 10^{-5} M	Chromosomal abberations	+	Stella et al., 1982
		$CrCl_3$	+6	10^{-6} to 10^{-3} M		-	
Clastogenic	CHO cells	$K_2Cr_2O_7$	+6	0.1 and 0.3 µg/mℓ	Sister chromatid exchange	+	Levis and Majone, 1979
		$Na_2Cr_2O_7$	+6	0.1 and 0.3 µg/mℓ		+	
		K_2CrO_4	+6	0.25 µg/mℓ		+	
		Na_2CrO_4	+6	0.25 µg/mℓ		+	
		CrO_3	+6	0.1 and 0.25 µg/mℓ		+	
		$CrCl_3$	+3	5 and 50 µg/mℓ		-	
		$Cr(NO_3)_3$	+3	50 and 150 µg/mℓ		-	
		$KCr(SO_4)_2$	+3	150 µg/mℓ		-	
		$Cr(COOCH_3)_3$	+3	5 and 20 µg/mℓ		-	
Clastogenic	Don Chinese hamster cells	$CrCl_3 \cdot 6H_2O$	+3	32 µg/mℓ	Sister chromatid exchange	+	Ohno et al., 1982
		$Cr_2(SO_4)_3 \cdot 4H_2O$	+3	6 µg/mℓ		-	
		CrO_3	+6	0.32 µg/mℓ		+	
		K_2CrO_4	+6	0.8 µg/mℓ		+	
		$K_2Cr_2O_7$	+6	0.8 µg/mℓ		+	
Clastogenic	cultured human lymphocytes	$K_2Cr_2O_7$	+6	0.025 to 0.1 µg/mℓ	Sister chromatid exchange	+	Gomez-Arroyo et al., 1981
		$CaCrO_4$	+6	0.01 to 0.02 µg/mℓ		+	
		CrO_3	+6	0.025 to 0.1 µg/mℓ		+	
Clastogenic	polychromatic erythrocytes from NMRI mice	K_2CrO_4	+6	2 x 48.5 mg/kg, IP	Micronucleus test	+	Wild, 1978
				2 x 24.25 mg/kg, IP		+	
				2 x 12.12 mg/kg, IP		-	
Clastogenic	gel cells from *Boleophthalmus dussumieri*	$Na_2Cr_2O_7$	+6	1 or 5 mg/kg IM	Chromosomal aberrations	+	Krishnaja and Rege,
				24 or 30.5 ppm in the aquarial water		+	
Clastogenic	human lymphocytes	CrO_3	+6	Occupational exposure	Sister chromatid exchange	+	Stella et al. 1982
Clastogenic	human lymphocytes	CrO_3	+6	Occupational exposure	Chromosomal aberrations	+	Sarto et al., 1982

* = Refer to text for further information.
IP = Intraperitoneal injection
IM = Intramuscular injection

caution in interpreting these findings. Casto et al. (1979), using a different experimental system, demonstrated that the Cr(VI) compounds, $CaCrO_4$, K_2Cr_4, and $ZnCrO_4$, at concentrations of 0.006, 0.01, and 0.01 mM enhanced the virally induced transformation frequency of primary embryo hamster cells. The increase in transformations was ≈2 for the Ca and K salts, and 4 for the Zn salt. Other metals assayed that had no indication from the literature of genotoxic properties did not enhance the rate of viral transformation.

Increase in cell transformation has also occurred in cells isolated from hamster embryos exposed in utero to Cr(VI) (DiPaolo and Casto, 1979). Initially, it was demonstrated that $NaCrO_4 \cdot 4H_2O$ at levels of 1.0, 2.5, and 5.0 μg/mℓ increased the transformation frequency of isolated hamster embryo cells in culture to 0.7, 2.1, and 3.48%, respectively. Following this initial study, pregnant Syrian golden hamsters (number not reported) were given intraperitoneal injections of $NaCrO_4$ at 2.5 mg/100 g body weight on day 11 of gestation. It was reported that cells isolated from embryos excised 2 days later produced elevated numbers of transformed colonies; however, the data were not presented for these studies. It was concluded that transplacental exposure to chromate resulted in alterations of fetal cells.

A number of studies have also demonstrated that exposure of cells in culture to either Cr(VI) or (III) compounds produces chromosomal aberrations. Raffetto (1977) exposed BALB/c mouse cells to $CrCl_3$(III) and $K_2Cr_2O_7$(VI) for either 48 or 96 hours. Increase in the number of chromosomal aberrations was noted for Cr(VI) at a level of 0.1 μg/mℓ, but not for Cr(III) at the same level after a 48 hour exposure; however, with 96 hours of exposure, Cr(III) at 0.4 μg/mℓ (0.04 μg/mℓ was also tested) and Cr(VI) at 0.1 and 0.015 μg/mℓ produced significant ($P<0.05$) increases in the number of chromosomal aberrations. Newbold et al. (1979) also detected dose dependent chromosomal damage with $K_2Cr_2O_7$ at levels between 0.35

and 0.8 μg/mℓ in V79 cells. Similar results were reported by Levis and Majone (1979), in which both Cr(III) compounds [$CrCl_3$, $Cr(NO_3)_3$, $KCr(SO)_4)_2$, and $Cr(COOCH_3)_3$] and Cr(VI) compounds ($K_2Cr_2O_7$, $Na_2Cr_2O_7$, K_2CrO_4, Na_2CrO_4, CrO_3, and $CaCrO_4$) produced increases in chromosomal aberrations in CHO cells in culture. Again, Cr(VI) compounds were more active, with positive responses obtained at doses of 0.1 to 0.5 μg/mℓ, while marginal positive responses with Cr(III) occurred at doses of 5 to 150 μg/mℓ. Although both valence states produced chromosomal aberrations, only Cr(VI) induced increases in sister chromatid exchange, and even the increase observed with Cr(VI) was small in comparison to the response elicited by the positive control, Mitomycin C. Sister-chromatid exchange was also observed by Ohno et al. (1982) in Don Chinese hamster cells following treatment with the Cr(VI) compounds CrO_3, K_2CrO_4, and $K_2Cr_2O_7$ at concentrations of 0.32, 0.8, and 0.8 μg/mℓ, respectively. The Cr(III) compounds $CrCl_3 \cdot 6H_2O$ and $Cr_2(SO_4)_3 \cdot 4H_2O$ were less active than the Cr(VI) compounds at levels of 32 and 6 μg/mℓ, respectively, with the increases due to the sulfate not significantly elevated over control values. Again, as in the previous study, the levels of chromium induced sister-chromatid exchange was 10 times less than that of the positive control, mitomycin C. However, in the study by Umeda and Nishimura (1979), only the Cr(VI) compounds, $K_2Cr_2O_7$ and CrO_3, produced chromosomal aberrations in mouse FM3A cells, while K_2CrO_4(VI) was negative even at high concentrations. It is not clear why Cr(III) was negative in this study, although these results may reflect a difference in sensitivity of these cells.

The effectiveness of chromium compounds in producing chromosomal aberrations was affected by the valence state of the compound. Tsuda and Kato (1977) demonstrated that 0.5 μg/mℓ of $K_2Cr_2O_7$ produced chromosomal aberrations in 51% of hamster embryo metaphases examined; however, addition of the reducing agent, Na_2SO_3, at a level of 0.645 μg/mℓ resulted in a decrease in abnormal metaphases to 6%. This provides further evidence that Cr(VI) was more active than Cr(III) in producing chromosomal aberrations.

Nakamuro et al. (1978) used peripheral blood human leukocytes in short-term culture to elevate the clastogenic effects of a number of Cr(VI) and Cr(III) salts. Following isolation and 24 hours of culture, the cells were exposed to Cr(VI) ($K_2Cr_2O_7$, K_2CrO_4) and Cr(III) ($Cr(CH_3COO)_3$, $Cr(NO_3)_3$, $CrCl_3$) chromium at the respective concentrations of 0.125 to 4, 0.5 to 8, 4 to 32, 32, and 32×10^{-6} M. Significant increases ($P<0.01$) in total chromosomal aberrations were observed at the higher doses with all compounds except $Cr(NO_3)_3$(III) and $CrCl_3$(III). It was apparent that human leukocytes responded similarly to other cultured cells in regard to sensitivity to chromium induced chromosomal aberrations.

In vivo clastogenic activity of $KCrO_4$ has been observed in mice by the micronucleus test (Wild, 1978). NMRI mice (4 animals of each sex) were treated by two intraperitoneal injections of 0.0, 12.12, 24, 25, or 48.5 mg/kg of K_2CrO_4 in saline, followed in 6 hours by examination of bone marrow for micronucleus-containing erythrocytes. Of the 1000 cells examined per mouse, there were 3.1, 4.8, 9.6, and 15.0% micronucleated polychromatic erythrocytes in the control and treated animals, respectively. The responses in the two highest dose groups represent significant increases over control values. Chromosomal aberrations, including breaks, fragments, rings, exchanges and unclassified makers, were observed in the gills of the fish Boleophthalmus dussumieri after exposure to sodium dichromate(VI) (Kushnaja and Rege, 1982). The number of total aberrations increased from 1 to 6 and 16 after intramuscular injection of $Na_2Cr_2O_7$ at doses of 0.0, 1, and 5 mg Cr/kg, respectively. Increases in total aberrations of 0, 7, and 7 were also observed when the fish were maintained in water for 96 hours containing chromium at levels of 0.0, 24.0, or 30.5 ppm (the high dose level killed 50% of the fish). Other heavy metals and mitomycin C also produced chromosomal aberrations in this test system.

Human lymphocytes exposed either in vitro to chromium or isolated from workers occupationally exposed to chromium have been used to investigate chromium induced chromosomal damage. Increase in both sister chromatid exchange and chromosomal aberrations were observed when cultured human lymphocytes were exposed to the Cr(VI) compounds $K_2Cr_2O_7$, $CaCrO_4$, and CrO_3 (Gomez-Arroyo, 1981; Stella et al., 1982; Littorin et al., 1983); however, the Cr(III) compound, $CrCl_3$, was totally inactive (Stella et al., 1982) in this assay. In blood samples taken from workers in the chromium plating industry (Stella et al., 1982; Sarto et al., 1982) there were increases in chromosomal changes in the peripheral lymphocytes. Stella et al. (1982) obtained blood samples from 12 male workers and 10 control donors not exposed to chromium. There was no significant difference in the incidence of sister chromatid exchange in the 5 older workers (24 to 47 years of age); however, in the 7 youngest workers (17 to 23 years of age) there was a significant increase. The control subjects had an age associated increase in sister chromatid exchange, while the level in the exposed population appeared constant. Sarto et al. (1982) studied the peripheral lymphocytes of workers in two "hard" plating (one of the plants was the same as that studied by Stella et al., 1982) and two "bright" plating industries. In the "hard" plating industry, exposure was to chromium alone, while in the "bright" plating industry the workers were also exposed to nickel. As in the previous study, the younger workers had significant increases in chromosomal aberrations while the number of aberrations was not significantly elevated from control levels in the older workers. There was also a positive association between urinary chromium levels and the number of chromosomal aberrations in the two "hard" plating plants. The authors concluded that these data support the genotoxicity of the soluble Cr(VI) ion.

Venier et al. (1982) tested 10 Cr(III) compounds used in leather tanning, and one Cr(III)-chromite compound used as a pigment, for cytotoxicity (inhibition and growth and survival of cultured hamster cells), mutagenicity (S. typhimuriam), and clastogenic activity (chromosomal aberrations and SCEs). Generally, the trivalent compounds were only slightly cytotoxic. The hexavalent reference compounds, potassium dichromate, had a cytotoxic activity at 0.5 µg Cr(VI)/mℓ (ID_{50} for growth) and 0.2 µg Cr(VI)/mℓ (LD_{50} for cell survival). For the trivalent compounds, 100 to 500 times greater amounts were required to inhibit growth or destroy the cells. Only two trivalent compounds (chromite and chromium nitrate) were mutagenic; however, both compounds were contaminated with Cr(VI). Again, the frequency of SCEs was increased only for the Cr(III) contaminated with Cr(VI). Only the chromium nitrate reference compound and the weakly contaminated Cr(III) compounds caused an increase in chromosomal aberrations. The authors concluded that hexavalent chromium compounds were primarily responsible for the genotoxic effects of chromium.

In contrast, Elias et al. (1983) found that a range of 9 to 136 µg Cr(III)/mℓ caused a significant increase in SCEs, but, as seen by Venier et al. (1982) and Ohno (1982), this only occurred at trivalent chromium levels 300 to 1000 times higher than that required by Cr(VI) compounds.

7.3.4. Summary. In vitro and in vivo assays of genotoxicity have tried to clarify the mechanism of chromium carcinogenicity and have supported the potential for Cr(VI) to be the active carcinogenic species. Cr(VI) has demonstrated consistently postive mutagenic activity in a number of bacterial systems. This activity was demonstrated in the absence of a metabolic activation system. In the presence of a metabolic activation system, the mutagenic activity of Cr(VI) disappeared. Because chromium shows only marginal, if any, mutagenic activity after metabolic activation, it was suggested that the mammalian enzymes or cofactors in the activation system reduced Cr(VI) to Cr(III). Both Cr(III) and Cr(VI) have been demonstrated to interact with DNA in bacterial assays, and Cr(VI) has inhibited DNA synthesis and increased unscheduled DNA synthesis in mammalian cells in culture. In *in vitro* studies, both Cr(III) and Cr(VI) have increased the infidelity of DNA replication. As observed with interaction with DNA, both valences of chromium have been demonstrated to produce clastogenic effects in mammalian cells with Cr(VI) being more active than Cr(III). The effects observed included a variety of chromosomal aberrations, sister chromatid exchange, and the appearance of micronuclei in polychromatic erythrocytes. Increased chromosomal damage also has been observed in human lymphocytes cultured from subjects occupationally exposed to chromium. For all the observed genotoxic effects, it has been suggested that Cr(III) may be the predominant intracellular species as a result of the reduction of absorbed Cr(VI) by cellular components.

7.4. DEVELOPMENTAL TOXICITY AND OTHER REPRODUCTIVE EFFECTS

7.4.1. Developmental Toxicity. Chromium salts have been shown to be teratogenic and embryotoxic in mice and hamsters following intravenous or intraperitoneal injection.

In one study, golden hamsters were given single intravenous CrO_3(VI) injections of 5, 7.5, 10, or 15 mg/kg on the eighth day of gestation (Gale, 1978). Treatment groups were as follows: 15 dams exposed (5 mg/kg), 18 dams exposed (7.5 mg/kg), 21 dams exposed (10 mg/kg), and 4 dams exposed (15 mg/kg). In all but the 5 mg/kg group, dams exhibited signs of chromium toxicity, including weight loss and tubular necrosis of the kidneys. The highest dose was lethal to 75% of the dams.

Chromium given on the eighth day of gestation resulted in increased fetal wastage at doses of $\geq$7.5 mg/kg (statistics not reported). The major external anomaly noted was cleft palate. Incidence was significantly elevated above the control level for all treated groups (method not stated). The primary internal abnormality recorded was hydrocephaly, with an increased incidence noted in all treatment groups. In addition, a wide range of skeletal defects was noted.

In a second study, golden hamsters were given intravenous CrO_3 of 8 mg/kg on day 7, 8, 9, 10 or 11 (Gale and Bunch, 1979). Six pregnant female hamsters were treated in each time-group with three concurrent controls. Fetal death was greatest in litters treated on the seventh day of gestation when there was an 84% incidence of resorptions. Resorption incidence was elevated to a small degree on days 8 and 9 (20 and 13%, respectively), but was not affected on days 10 and 11.

As in the previous study, cleft palate was the primary external abnormality recorded, occurring most frequently in litters from dams exposed on day 7 of gestation and at elevated incidence rates with respect to controls on days 8 and 9, but not on days 10 and 11 (determined based on tables of binomial confidence limits). The only internal abnormalities noted were kidney defects in groups exposed on days 7 or 8 of gestation. Group sizes were too small to establish a significant difference from controls. As in the previous study, treated females exhibited signs of chromium toxicity which included body weight loss and tubular necrosis of the kidneys.

In a continuation of this work, Gale (1982) tested Cr(III) in noninbred (LVG) and inbred (CB, LHC, SDH, MHA, and PD4) strains of hamsters for reproductive and teratological effects. The dams (10 animals/group) were treated by intravenous injection on the 8th day of gestation with a single dose of 8 mg/kg of Cr(III). On termination at day 15 of gestation, it was determined that strains CB, LHC, and PD4 were resistant to any adverse effects of treatment. In the other strains, LVG, LSH, and MHA there was an increased incidence of cleft palate (33, 18, and 15 animals, respectively, while control groups had no more than 1 pup/group with cleft palate) and other external abnormalities. The dams of the strains with the highest incidences of fetal abnormalities also lost weight during the period of gestation following treatment. Strain differences were reported for the reproductive effects of other metal compounds in these animals; however, the genetic mechanism which results in these differences in susceptability was not understood.

Matsumoto et al. (1976) administered chromium chloride (+3), 19.52 mg/kg (as Cr), intraperitoneally to ICR mice on day 7, 8, or 9 of gestation. Eight control dams received a saline injection. Treatment group sizes were 5, 6, and 7 on days 7, 8, and 9, respectively. The embryonic and fetal death rates were elevated following treatment on days 8 and 9 ($P<0.001$, method not stated). The incidence of external malformations was significantly greater than in controls in litters of dams exposed on day 8 of gestation ($P<0.001$, method not stated). Recorded anomalies included exencephaly and open eyelids. In addition, there was a small increase in skeletal defects in litters from dams treated on days 8 and 9.

In a second experiment, pregnant dams were given intraperitoneal injections of chromium chloride as dose levels of 9.76, 14.64, 19.52, or 24.4 mg/kg as Cr on day 8 of gestation. Group sizes were: control (11 dams), 9.76 mg/kg (13 dams), 14.64 mg/kg (13 dams), 19.52 mg/kg (7 dams), 24.4 mg/kg (9 dams). Fetal weights were significantly reduced in all treatment groups ($P<0.05$, method not stated). The incidence of external malformations was significantly greater than control values for the 14.64 mg/kg dose group and all higher dose groups ($P<0.05$, method not stated). Anomalies with greatest incidence in rats were open eyelids, exencephaly, and acephalia. In addition, skeletal defects were noted in these same groups.

Iijima et al. (1979) dosed pregnant ICR mice with CrO_3(VI) by subcutaneous injection. Mice were injected with a single 10 or 20 mg/kg dose on day 7, 8, 9, 10, or 11 of gestation. The 20 mg/kg dose was lethal to one-third of the dams. In this group, a significant increase in external anomalies was recorded in litters from dams exposed on day 8 of gestation. Cleft palate was the primary abnormality. In addition, increased fetal and embryonic death rates were noted in groups exposed to 20 mg/kg on day 8 or day 11.

The studies discussed in the text above are summarized in Table 7-24.

Iijima et al. (1983) found that radiolabeled chromium levels in fetal tissues increased, while levels in maternal blood decreased after single intraperitoneal injections of 9.8 mg Cr ($^{51}CrCl_3$)/kg body weight at gestation day 8. Their findings indicated that $CrCl_3$ could affect embryos directly and cause neural tube defects. They noted also that pyknotic cells on the neural plate could indicate the development of exencephaly.

Danielsson et al. (1982) found considerable differences between Cr(III) and Cr(VI) in their distribution in embryonic and fetal uptake. Forty-two pregnant mice received single doses (5 µg/kg i.v.) of $CrCl_3$ or $Na_2Cr_2O_7$ on days 8 to 18 of gestation. On day 13 of gestation, embryonic concentrations were 12% Cr(VI) and 0.4% Cr(III). Fetal concentration of both compounds increased with gestational age, probably binding to fetal calcified bone, which develops on day 14. According to the authors, it appeared that Cr(VI) occurred at sufficiently high fetal concentrations to cause direct effects on embryonic sturctures, i.e., delay in skeletal development by inhibition of cartilage formation. Cr(III), on the other hand, was not detected in embryonic structures during early gestation, but it could act on placental structures and thereby affect fetal development.

As discussed previously (Section 5.2.1.), there are limited data demonstrating transfer across the placenta. It should be pointed out that most

TABLE 7-24

Teratogenic and Fetotoxic Effects of Chromium

Compound	Route	Species	Dose	Fetal Effects	Maternal Effects	Reference
CrO_3	i.v.	hamster	5, 7.5, 10, or 15 mg/kg on day 8 of gestation	increased fetal death in 7.5, 10, and 15 mg/kg groups, increased incidence of cleft palate in all groups, hydrocephaly and skeletal defects	depressed weight gain and kidney tubular necrosis at all doses above 5 mg/kg	Gale, 1978
CrO_3	i.v.	hamster	8 mg/kg on day 7, 8, 9, 10, or 11 of gestation	increased fetal death following administration on day 7, increased incidence of cleft palate following administration on days 7, 8, or 9	weight loss, tubular necrosis of kidneys	Gale and Bunch, 1979
$CrCl_3$	i.p.	mouse	9.76, 14.64, 19.52, or 24.4 mg/kg on day 8 of gestation	depression of fetal weights in all Cr treated groups, increase in rate of external abnormalities for groups treated with 14.64, 19.52, or 24.4 mg/kg	not reported	Matsumoto et al., 1976
CrO_3	i.v.	hamsters (strain LVG)	8 mg/kg on day 8 of gestation	increased incidence of cleft palate	body weight loss	Gale, 1982
		hamsters (strain CB)	8 mg/kg on day 8 of gestation	no effect	no effect	

TABLE 7-24 (cont.)

Compound	Route	Species	Dose	Fetal Effects	Maternal Effects	Reference
		hamsters (strain LHC)	8 mg/kg on day 8 of gestation	no effect	no effect	
		hamsters (strain LSH)	8 mg/kg on day 8 of gestation	increased incidence of cleft palate	body weight loss	
		hamsters (strain PD4)	8 mg/kg on day 8 of gestation	no effect	no effect	
		hamsters (strain MHA)	8 mg/kg on day 8 of gestation	increased incidence of cleft palate	body weight loss	
CrO_3	s.c.	mouse	10 or 20 mg/kg on day 7, 8, 9, 10, or 11 of gestation	increase in external malformations in 20 mg/kg group when dosed on day 8, as well as increase fetal death when dosed on day 8 or 11	lethal to 1/3 of dams	Iijima et al., 1979

TABLE 7-24 (cont)

Compound	Route	Species	Dose	Fetal Effects	Maternal Effects	Reference
$CrCl_3$	i.p.	mouse	9.8 mg/kg on day 8 of gestation	Cr increased gradually and peaked at 24 hr, exceeding maternal blood Cr level.	Maximum blood Cr at 4 hr post-i.p. and gradually decreased	Iijima et al., 1983
$CrCl_3$	i.p.	mouse	19.5 mg/kg/day	Pyknotic cells in neuroepithelium of neural ectoderm in 2 of 5 embryos after 4 hr; in all 5, after 8 hr.	NR	Iijima et al., 1983
$CrCl_3$	i.v.	mouse	10 mg/kg on days 13 and 16 of gestation	Fetal Cr(III) was 0.4% of maternal serum Cr 1 hr post-i.v.; high accumulation of Cr in yolk sac placenta. In late gestation, Cr accumulated in calcified areas of fetal skeleton.	NR	Danielsson et al., 1982
		[*in vitro*]	0 to 15 μg/mℓ	No overt cytotoxicity at 15 μg/mℓ in embryonic cell cultures (chick cells).	NA	Danielsson et al., 1982
$Na_2Cr_2O_7$ [Cr(VI)]	i.v.	mouse		Fetal Cr(VI) was 12% of maternal serum Cr 1 hr post-i.v. In late gestation, Cr accumulated in calcified areas of fetal skeleton.	NR	Danielsson et al., 1982
Cr(VI)		[*in vitro*]	0.1 to 0.28 μg/mℓ	Affected cartilage production at ≈0.1 μg/mℓ in embryonic cell cultures (chick cells).	NA	Danielsson et al., 1982

i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous

NR = Not reported; NA = Not applicable

studies have sampled fetuses near the end of gestation, not early in organogenesis when the fetus may be more susceptible to teratogens. Further research is clearly indicated to further define the nature and extent of possible chromium teratogenesis and embryo toxicity.

7.4.2. Other Reproductive Effects. Behari et al. (1978) examined the effects of chromium on testicular tissue in rabbits. Animals were injected intraperitoneally with chromium nitrate or potassium dichromate at doses of 2 mg/kg for 3 or 6 weeks. Both forms of chromium resulted in a decrease in testicular succinic dehydrogenase at 3 and 6 weeks. Adenosine triphosphatase was inhibited at both time points with both compounds, but the Cr(III) compound resulted in more severe depression. Acid phosphatase was significantly depressed at 6 weeks in animals given the trivalent salt.

The administration of Cr(III) resulted in thickening of the tunia albuginea and congestion of blood vessels following 3 weeks of treatment. In addition, cells in the seminiferous epithelium showed degenerative changes. At the 6 week time point, these degenerative changes were more pronounced, and there was a complete absence of spermatocytes in the lumen. Cr(VI) produced mild edema of the interstitial tissue of the testes at 3 weeks. Following 6 weeks of exposure, edema was more marked and congestion of the blood vessels was noted. Although the seminiferous epithelium appeared normal, the tubules were devoid of spermatocytes.

Hopkins (1965) postulated that incorporation of chromium into sperm and subsequent passage into the epididymis may be a problem. This hypothesis is based upon observation of chromium uptake by testis, subsequent decline of testicular radioactivity, and subsequent increase in radioactivity in the epididymis (see Section 5.2.2.). Gross and Heller (1946) have reported sterility in rats exposed to zinc chromate and potassium chromate in the diet (Section 7.2.5.).

7.4.3. Summary. Chromium has adversely affected fetal development and male reproduction in experimental animals. Hamsters administered chromium trioxide intravenously on day 8 of gestation had an increased incidence of cleft palates in the young when examined on day 15 of gestation. The malformations were strain specific and associated with maternal toxicity. Studies on the mouse indicated that while some skeletal effects were present, increased incidence of cleft palate or fetal death were not observed. While several of the studies reported fetal malformations only where maternal toxicity was also present, not all studies reported data on maternal effects, so definitive conclusions concerning the correlation if any between fetal and maternal effects cannot be made at this time.

Other reproductive effects of chromium include testicular degeneration in rabbits receiving 2 mg/kg/day for 6 weeks of either Cr(III) or Cr(VI) compounds by intraperitoneal injection. The Cr(III) compound produced more severe effects in this study than did the Cr(VI) compound (Behari et al., 1978). The relevance of these observations to effects observed after environmental exposure is questionable, as is that of the previously discussed teratogenicity studies, since the routes of exposure were not natural. There is clearly a need for more relevant studies on the route of exposure than are presently available.

7.5. OTHER TOXIC EFFECTS OF CHROMIUM

The literature concerning chronic and subacute exposure to chromium consists primarily of reports of no observable effect levels (NOEL). Although the kidney and liver have been shown to be targets following acute exposures, reports of pathology in these organs following long-term exposure via relevant routes were not found. There are two reports which suggest effect levels following oral exposure; these studies are summarized in the following text. The numerous studies which suggest free standing NOAELs are of limited value as a result of experimental design and are summarized in Table 7-25.

Gross and Heller (1946) reported that 0.125% K_2CrO_4 in the feed of rats was tolerated without observable effects, 0.25% resulted in "subnormal condition", including rough coat and "subnormal" young born to treated animals. Doses of 0.5 and 1% resulted in diarrhea, rough dirty coats, and sterility. $ZnCrO_4$ adminis tered in the feed at levels of 0.125, 0.25, 0.5, and 1.0% resulted in subnormal appearance, rough and dirty coats, and sterility at all dose levels. Group sizes, duration of treatment, and criteria for determining sterility were not reported.

Ivankovic and Preussman (1975) administered Cr_2O_3 to rats in their feed. The compound was prepared by incorporating it into bread dough at levels of 2 or 5%. In a 2-year study (600 feeding days), it was estimated that for the 2% treatment level, males consumed 75 g/kg (25 g/animal) over the entire study period and females consumed 72 g/kg (18 g/animal); at the 5% treatment level, males consumed 180 g/kg and females 160 g/kg for the duration of the study. Body weights were monitored and animals were maintained on normal rations following the treatment period. At death, animals were autopsied and "all the important organs" were studied for micropathology. In addition, a 90-day study was conducted also using bread levels of 2 or 5%. In this study, urinary protein, sugar, bilirubin, blood, and sediment were monitored. During the last 30 days of the study, treated animals were mated and the number of viable young produced in each litter was recorded. At the end of treatment, blood samples were analyzed for

TABLE 7-25

Studies Suggesting NOAELS or NOELS

Species	Route	Compound	Dose	Duration	No. at Start	Endpoints Monitored	Result	Reference
mouse	drinking water	K_2CrO_4	100, 200, 300, 300, 400, or 500 ppm	N.S.	N.S.	general appearance, reproduction	NOEL for all doses	Gross and Heller, 1946
mouse	feed	$ZnCrO_4$	1%	N.S.	N.S.	general appearance, reproduction	NOEL	Gross and Heller, 1946
rat (young)	drinking water	K_2CrO_4	300 and 500 ppm	N.S.	N.S.	general appearance, reproduction	NOAEL; slight roughness of coal at 500 ppm	Gross and Heller, 1946
rat (young)	feed	K_2CrO_4	0.125%	N.S.	N.S.	general appearance, reproduction	NOEL	Gross and Heller, 1946
rat	feed	Cr_2O_3	0, 1, 2, or 5%	2 years	60/ group	gross and microscopic pathology, body weights	NOEL	Ivankovic and Preussman, 1975
dog	drinking water	K_2CrO_4	0.45, 2.25, 4.5, 6.75, or 11.2 ppm	4 years	2/group	urinalysis including albumin, acetone, bile pigments glucose, indican erythrocytes, and specific gravity; gross and microscopic pathology of adrenals, bone marrow, brain, heart, intestine, kidney, liver, lung, mesenteric lymph node, parathyroid, pancreas, spinal cord, spleen, stomach, thyroid, and tonsils; weights of liver spleen and kidney	NOEL	Anwar et al., 1961

TABLE 7-25 (cont.)

Species	Route	Compound	Dose	Duration	No. at Start	Endpoints Monitored	Result	Reference
rat	drinking water	K_2CrO_4	0, 0.45, 2.2, 4.5, 7.7, 11 and 25 ppm	12 mo	highest dose 9 females, 12 males control 10 of each sex, all other groups, 8 males, 8 females	clinical blood chemistry, body weights gross and microscopic pathology	NOEL	MacKenzie et al., 1958
rat	drinking water	$CrCl_3$	0, 25 ppm	12 mo	12 males, 9 females	clinical chemistry body weights, gross and microscopic pathology	NOEL	MacKenzie et al., 1958
cat	feed	chromium carbonate, chromium phosphate	50 to 100 mg/cat/day	1 to 3 mo	10	organ weights macroscopic pathology microscopic pathogy of lung, heart, liver, stomach, spleen, pancreas, kidney, brain, sketal muscles	NOEL	Akatsuka and Fairhall, 1934
cat	inhalation	chromium carbonate dust	from 3.3 to to 83 mg/m^3 average 58.3 mg/m^3	86 sessions which varied from 10 to 60 min and averaged 28 min for one cat and 57 min for the other	2	gross and microscopic pathology	NOEL	Akatsuka and Fairhall, 1934

blood sugar, serum protein, serum bilirubin, and haemoglobin. Erythrocytes and leukocytes were counted. Liver, spleen, kidney, brain, and ovaries were weighed, fixed, and sectioned at autopsy. In addition, lung, heart, pancreas, stomach, small intestine, and urinary bladder were also fixed and sectioned.

In the 90-day study, the only treatment related effect was a depression of spleen and liver weights. Spleen weights appeared to be depressed at both doses in both sexes. Liver weights appeared to be depressed in both dose groups for females and in high dose males. Statistical analyses were not reported. In the 2-year study, no treatment related effects were reported.

Berry et al. (1978) examined localization of chromium within the kidney. Rats were dosed by intraperitoneal injection with 0.1 mg potassium dichromate/100 g body weight. Doses were given 5 times per week for 8 months. Chromium was localized within cells of the proximal renal tubules, specifically within lysosomes. Chromium was retained throughout most of the study period, being eliminated only when necrosis involved the entire cytoplasm of the tubule cells.

7.5.1. Respiratory Effects. Steffee and Baetjer (1965) exposed rabbits, guinea pigs, rats, and mice to mixed chromate dust via inhalation or intratracheal injection. Inhalation exposures were conducted 5 hours/day, 4 days/week throughout the lifespan of the animals. The average air concentration was estimated to be 3 to 4 mg of CrO_3/m^3. The average weekly exposure was estimated to be 53, 44, and 49 mg/hour for rabbits, guinea pigs, and rats, respectively. The following exposure related effects were documented in the lungs of exposed animals. Fifteen percent of the rabbits and rats in the inhalation exposures, and rabbits and guinea pigs in the intratracheal groups exhibited granulomata. This lesion was found in only one control rat and in none of the rabbits or guinea pigs. The incidence of alveolar and interstitial inflammation was greater than controls in guinea pigs exposed via both routes. Exposure related effects in liver, kidney, and spleen were not found.

Nettesheim et al. (1971) exposed mice to calcium chromate dust 5 hours/day, 5 days/week for life. The exposure concentration was 13 mg/m^3 of $CaCrO_4$. This exposure concentration depressed weight gains. Exposed animals showed marked alterations in the epithelium of the bronchial tree after 6 months of exposure. These alterations were graded from epithelial necrosis and atrophy to marked hyperplasia. In addition, bronchiolization of alveoli (bronchiolar cells lining alveolar walls) was observed. Another frequently observed effect was alveolar proteinosis. In addition to lung effects, morphological changes were noted in the tracheal submandibular lymph nodes. After 2 years of exposure, spleen and liver were atrophied. Ulcerations in the stomach and intestinal mucosa were noted occasionally.

Early historical recognition of the ulcerative property of Cr(VI) compounds in humans is evidenced by several studies on the subject (Becourt and Chevallier, 1863; Delpech and Hillairet, 1869; Legge, 1902).

Bloomfield and Blum (1928) reported on 23 men employed in six chromium plating plants in the United States. Their findings are presented in Table 7-26. They concluded that continuous daily exposure to chromic acid at concentrations >0.1 mg/m^3 is likely to cause nasal tissue injury. As can be seen from Table 7-26, no concentrations <0.12 mg/m^3 were observed; hence, injury to nasal tissue caused by lower concentrations could not be ruled out.

Four of 33 chromium platers were found to have septal perforation, although the highest measured concentration of chromium trioxide in the workplace was 0.003 mg/m^3. Of the 33 workers, six had what the author considered to be normal noses. He suggested that in view of the low chromium concentration, the lesions

TABLE 7-26

Clinical Findings in Workers Employed in Chromium-Plating Plants[a]

Case	Occupation	Time Employed in Chromium-Plating Room, mo	Time Over Tank, h/d	Approximate CrO_3 Exposure, mg/m^3	Perforated Septum[b]	Ulcerated Septum[b]	Inflamed Mucosa[b]	Nosebleed	Chrome Holes
1	Chromium plater	6	4	1.5	++	-	++	Yes	Yes
2	Chromium plater	20	4	2.8	++	-	+	Yes	Yes
3	Foreman plater	7	2	2.5	-	++	++	Yes	No
4	Foreman plater	8.5	3	2.5	-	++	++	Yes	No
5	Chromium plater	3.5	4	5.6	-	++	++	Yes	Yes
6	Chromium plater	0.75	7	0.12	-	-	++	Yes	Yes
7	Chromium plater	0.25	7	0.12	-	-	++	Yes	No
8	Chromium plater	7	7	0.12	-	-	++	Yes	No
9	Chromium plater	3	7	0.12	-	-	++	No	Yes
10	Chromium plater	36	4	0.2	-	-	++	No	No
11	Chromium plater	5	6	0.12	-	-	+	Yes	Yes
12	Chromium plater	0.75	6	0.12	-	-	+	No	No
13	Chromium plater[c]	12	4	2.8	-	-	-	No	No
14	Chromium plater	0.67	2	2.8	-	-	-	No	No
15	Nickel plater[d]	1.5	0	?	-	+	+	Yes	No
16	Racker	8	0	?	+	-	+	Yes	No
17	Racker	0.75	0	?	-	-	+	No	No
18	Racker	0.75	0	?	-	-	+	No	No
19	Wiper	1.5	0	?	-	-	+	No	No

TABLE 7-26 (cont.)

Case	Occupation	Time Employed in Chromium-Plating Room, mo	Time Over Tank, h/d	Approximate CrO_3 Exposure, mg/m^3	Perforated Septum[b]	Ulcerated Septum[b]	Inflamed Mucosa[b]	Nosebleed	Chrome Holes
20	Foreman[e]	0	0	0	-	-	+	No	No
21	Foreman[e]	0	0	0	-	-	+	No	No
22	Clerk[e]	0	0	0	-	-	-	No	No
23	Inspector[e]	0	0	0	-	-	+	No	No

[a] Source: NAS, 1974a

[b] ++, marked; +, slight; -, negative.

[c] Used vaseline in nose.

[d] Cyanide burns

[e] Worked in other departments of factory

mo = month; h = hour; d = day

that resulted were due to exposure to periodic high concentrations of chromium trioxide that occurred when ventilation of the tank failed (Lumio, 1953).

Anodizing operators exposed to concentrations of chromic acid mist ranging from 0.09 to 1.2 mg/m^3 (as CrO_3) developed ulceration of the nasal passages and atrophic rhinitis (Gresh, 1944; Zvaifler, 1944).

The United States Public Health Service conducted a study on workers in seven chromate-producing plants in the early 1950's. The results are shown in Table 7-27. Unfortunately, the results of the physical examinations on the workers were not related to chromium exposures, and hence, the data are of limited usefulness (Federal Security Agency, 1953).

Mancuso (1951) reported on physical examinations of a random sample of 97 workers from a chromate-chemical plant. It can be seen from the results which are presented in Table 7-28, that 61 of 97 workers (63%) had septal perforation. The data suggested to the author that Cr(III) may be partly responsible for the perforations; however, later studies have not provided support for this theory.

The results of examinations of nine workers in a chrome-plating plant are shown in Table 7-29. Analyses of air samples showed chromium concentrations of 0.18 to 1.4 mg/m^3. Some degree of nasal septal ulceration was seen in 7 of the 9 men, with 4 of 7 demonstrating frank perforations (Kleinfeld and Russo, 1965). Unfortunately, the effects of chromium for a specific length of time at a fixed concentration were not studied.

In a Russian study conducted by Kuperman (1964), 10 apparently normal persons were exposed to Cr(VI) aerosol concentrations of non-reported composition ranging from 0.0015 to 0.04 mg/m^3. Air containing Cr(VI) at 0.01 to 0.024 mg/m^3 sharply irritated the nose when inhaled for short periods of time. The most sensitive person responded at a chromium concentration of 0.0025 to

TABLE 7-27

Perforation of Nasal Septum in Chromate Workers*

Time Worked in Chromate Industry	All Workers			White Workers			Nonwhite Workers		
	Total No.	Workers with Perforation No.	Workers with Perforation %	Total No.	Workers with Perforation No.	Workers with Perforation %	Total No.	Workers with Perforation No.	Workers with Perforation %
<6 months	41	1	2.4	32	0	0	9	1	11.1
6 months to 3 years	117	46	39.3	89	28	31.5	28	18	64.3
3 to 10 years	370	205	55.4	235	104	44.3	135	101	74.8
≥10 years	369	257	69.6	297	190	64.0	72	67	93.1
TOTAL	897	509	56.7	653	322	49.3	244	187	76.6

*Source: NAS, 1974

TABLE 7-28

Perforation of Nasal Septum in Chromate Workers*

Ratio of insol Cr^{+3} to sol Cr^{+6}	Chromium Concentration, mg/m^3 (as Cr)	No. Workers Examined	Workers with Septal Perforation	
			No.	%
Workers in plant				
≤1.0:1	≤0.25	4	2	50
	0.26 to 0.51	7	3	43
	≤0.52	8	4	50
1.1 to 4.9:1	≤0.25	9	7	78
	0.26 to 0.51	32	20	63
	≥0.52	15	11	73
≥5.0:1	≤0.25	7	2	29
	0.26 to 0.51	2	1	50
	≥0.52	13	11	85
TOTAL		97	61	63
Office workers	0.06	4	0	0

*Source: NAS, 1974
insol = insoluble; sol = soluble

TABLE 7-29

Nasal Medical Findings in a Chromium-Plating Plant*

Case	Age, yr	Duration of Exposure, mo	Findings
1	30	6	Perforated septum
2	19	2	Perforated septum
3	19	12	Perforated septum
4	18	9	Perforated septum
5	47	10	Ulcerated septum
6	45	6	Ulcerated septum
7	23	1	Ulcerated septum
8	20	0.5	Moderate injection of septum and turbinates
9	48	9	Moderate injection of septum

*Source: NAS, 1974

0.004 mg/m^3; however, it was not known if this was a reaction to chromium or to the acidity of the aerosol.

Vigliani and Zurlo (1955) reported nasal septal perforation in workers exposed to chromic acid and chromates in concentrations of 0.11 to 0.15 mg/m^3. The lengths of exposure were not known. Otolaryngologic examinations of 77 persons exposed to chromic acid aerosol during chrome plating revealed 19% to have septal perforation and 48% to have nasal mucosal irritation. These people averaged 6.6 years of exposure to an air chromium concentration of 0.4 mg/m^3. In 14 persons, papillomas of the oral cavity and larynx were found. The diagnosis of papilloma was confirmed by histologic examination. There were no signs of atypical growth or malignant degeneration (Hanslian et al., 1967).

Cohen et al. (1974) have identified a serious health hazard among workers in a nickel-chrome plating area. Thirty-five of 37 (95%) employees exposed to atmospheric concentrations averaging 0.0071 mg/m^3 as total chromium were shown to have developed significant nasal pathology and skin lesions characteristic of exposure to chromic acid. The authors attributed the high incidence of adverse health effects to the lack of emphasis on the implementation of good industrial hygiene and personal hygiene. The mechanism postulated for the occurrence of the observed nasal damage resulted from either long-term exposure to levels of Cr(VI) below prescribed "safe" levels, or direct contact of the affected tissue resulting from inadequate personal hygiene practices.

The literature suggests that chromium compounds are responsible for a wide variety of other respiratory effects. Studies done by German investigators demonstrate mixed results from exposure to chromium compounds. Fischer (1911) and Lehmann (1914) reported that there were no marked clinical symptoms in persons exposed to chromate dust. Other German investigators (Alwens and Jonas, 1938; Fischer-Wasels, 1938; Koelsch, 1938; Lehmann, 1932; Mancuso, 1951) have reported that prolonged inhalation of chromate dust caused chronic irritation of the respiratory tract and resulted in such manifestations as congestion and hyperemia, chronic rhinitis, congestion of the larynx, polyps of the upper respiratory tract, chronic inflammation of the lungs, emphysema, tracheitis, chronic bronchitis, chronic pharyngitis, and bronchopneumonia. X-ray findings included enlargement of the hilar region (often on only one side), enlargement of the lymph nodes, increase in peribronchial and perivascular lung markings, and adhesions of the diaphragm. Letterer et al. (1974) and Lukanin (1930) stated that a characteristic pneumonoconiosis resulted from exposure to some chromates. correlation between workers exposed to a given airborne concentration of chromium (VI) and the development of harmful effects could not be made.

Cohen and Kramkowski (1973) and Cohen et al. (1974) examined 37 workers employed by a chromium-plating plant. Within 1 year of being employed, 12 workers experienced nasal ulceration or perforation. The airborne chromium (VI) concentrations ranged from <0.71 to 9.12 $\mu g/m^3$.

In a chromium plating plant where the maximum airborne chromium (VI) concentration was 3 $\mu g/m^3$, no ulcerated nasal mucosa or perforated nasal septa were found; however, half of the 32 employees had varying degrees of mucosal irritation (Markel and Lucas, 1973). This was not thought to be significant by the investigators, because the survey was carried out at the peak of the 1972 to 1973 influenza epidemic. The length of employment for the workers was as follows: ≥ 8 years, 15 workers; 4 to 8 years, 7 workers; 1 to 4 years, 4 workers; <1 year, 6 workers.

Machle and Gregorius (1948) reported an incidence of nasal septal perforation of 43.5% in 354 employees who worked in a chromate-producing plant that manufactured sodium chromate and bichromate. At the time of the study, airborne chromate concentrations ranged from 10 to 2800 $\mu g/m^3$. The plant has been in operation for at least 17 years, and some employees had probably worked in the plant when reverberatory furnaces, a prominent source of high chromate exposure, were used.

Chromium exposure in Australian shipyards, resulting from welding operations, has been reported by Bell (1976) to cause irritation to the nose and throat at welding fume ranging from 0.006 to 0.05 mg/^{3}. Lung biopsy specimens from welders confirmed the presence of severe pneumoconiosis similar to that reported by Stettler et al. (1977).

Various other disease states such as asthma have been attributed to chromium, but, in most cases, the etiologic relation to chromium is obscure because of the presence of other chemicals (NAS, 1974). Asthma was reported as a complaint among workers employed for >10 years in a ferrochromium plant in Norway (Broch, 1950). Bronchial asthma was also reported in Russian bauxite workers, where Cr(VI) was involved in the bauxite caking process (Budanova, 1976). A clinical test for the diagnosis of actual or imminent bronchial allergic reactions to Cr(VI) has been developed by Budanova and Makarova (1979). A correlation was established between the concentration of leukocyte agglomerates in blood stimulated by Cr(VI), with 3% for a healthy control group versus ≈16% for workers with heavy bronchial asthma. It appears, then, that chromium sensitization can occur after inhalation exposure as well as dermal exposure. In one chromium-alloy plant, four cases of pulmonary disease with nodular fibrosis and ventilatory impairment were reported by Princi et al. (1962), but no such cases were found in another similar plant (Pierce and Scheel, 1965).

Bovet et al. (1977) have suggested that workers exposed to chromium in electroplating operations have increased frequencies of obstructive respiratory disease. The lowest dynamic values of pulmonary function (e.g., vital capacity, forced vital capacity, forced expiratory volume, and forced expiratory flow) were reported for those workers displaying the higher urinary chromium levels. The effect of tobacco smoke on pulmonary function was minor compared to the effect attributed to chromium exposure. Forced expiratory flow and forced expiratory volume were the pulmonary functions decreased to the greatest extent as a result of occupational exposure to chromium. The total number of workers examined was 44, and no data on specific compounds, levels or duration of exposure were reported.

Capodaglio et al. (1975) demonstrated alterations in respiratory function among bichromate and chromic acid production workers. Observed changes in chest X-ray and respiratory function parameters were hypothesized to be the result of exposure to chromate, and the extent of the reduced pulmonary function was correlated to length of exposure. Data on the specific compounds and levels of exposure were not reported in the only available review of this study (NIOSH, 1975).

Workers in a chromite mine and concentration plant developed pulmonary markings (ground-glass types 1 and 2) that were attributed to chromite dust. However, free silica dust was also present in the air. No clinical or roentgenologic evidence of fibrosis was found in the chromate workers (Federal Security Agency, 1953). Royle (1975) has investigated the occurrence of various respiratory symptoms among British electroplaters exposed to chromic acid. A total of 997 platers and 1117 controls completed a Medical Questionnaire on Respiratory Symptoms. There was a significant ($p<0.025$) occurrence of attacks of bronchitis in platers (28.2%) compared to controls (23.7%). Platers also had significantly higher incidences of haemoptysis, perennial nasal catarrah, and Grade 2 habitual winter cough and Grade 2 winter phlegm production. Putative asthma was indicated in 13.1% of the platers at a 2.5% level of significance. Nasal and skin ulcers were significantly higher in platers. Smoking histories were comparable in intensity and longevity for both populations. No clinical testing or medical examinations were performed to verify the findings of the Medical Questionnaire. Controls were more frequently exposed to a variety of "dusts" in present or previous employment situations or both, and were also exposed to asbestos much more so than was the study population. Air samples taken between the years of 1969 and 1970 were <0.03 mg/m^3 in all but two cases (these were reported as <0.1 mg/m^3). Dust samples generally ranged from 0.3 to 97.0 mg/g, but were reported as high as 298 mg/g. Members of both the study and control populations were exposed to a variety of additional compounds that could cause similar symptoms (asbestos, cadmium, nickel), a circumstance that detracts from the overall quality of the study as does the use of medical questionnaires without any medical examinations to substantiate these subjective findings.

Lucas and Kramkowski (1975) have examined the occurrence of abnormal medical findings in a "hard" chromium electroplating processing plant. A total of 11 workers were screened for various medical complaints associated with exposure to chromic acid in electroplating operations. Average age of the workers was 39 years (range 22 to 54), with an average occupational exposure of 7.5 years (range 3 to 16 years). Average airborne chromium (VI) levels were reported as 0.004 mg/m^3, with a range of >0.001 to 0.020 mg/m^3, well within acceptable limits of the current NIOSH standards. Ventilation systems appeared to be functioning adequately, and work surfaces adjacent to the electroplating site were free from contamination by chromium trioxide, CrO_3. A summary of medical findings is found in Table 7-30. Despite the degree of protection offered by ventilation and protective clothing and equipment, workers displayed a significant number of adverse medical effects at presumably "safe" levels of exposure.

In addition, a fine nodular pneumoconiosis has been reported in a few chromite miners in South Africa (Sluis-Cremer and duToit, 1968). The available

TABLE 7-30

Medical Complaints of Workers in "hard" Chromium Electroplating Plant[a]

Frequency	Symptom
1	Nasal irritation
4	Nasal soreness[b,c]
6	Runny nose (chronic)[b,c]
4	Frequent nose bleeds
2	Ulceration of nasal septum
9	Scars indicating previous ulceration of the nasal septum
4	Perforated nasal septum
5	Chronic coughing episodes[d]
2	Pulmonary distress indicative of emphysema
7	Current skin sores
9	Scars indicating healed chrome ulceration on skin
5	Gastric distress
1	Chemical diabetes
1	Ocular pterygium on corneal conjunctiva
1	Advanced renal carcinoma (1967 diagnosis; 1968, one kidney removed; 1973, metastasized to second kidney; 1974, cobalt treatment

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[a] Source: Lucas and Kramkowski, 1975

[b] Previous to occurrence of nasal perforation.

[c] Two occurences were attributed to cold outdoor temperatures.

[d] Three individuals were reported as moderate to heavy smokers.

evidence suggests that the pneumoconiosis is due to deposition of chromite dust in the lung tissue, and that the condition is benign and caused no fibrosis. Other components of the ore, such as iron, may also have been responsible for the observed fine nodular pneumoconiosis.

7.5.2. Renal Effects Of Chromium. Several authors have reported kidney damage following the deliberate ingestion or therapeutic application of chromium compounds (Brieger, 1920; Godlman and Karotkin, 1935; Major 1922; Partington, 1950; Rambousek, 1913). Twelve persons died after the application of anti-scabietic ointment in which sulfur had been replaced with Cr(VI). Necrosis of the skin developed at sites of application and was followed or accompanied by nausea, vomiting, shock, and coma. Urinalysis revealed albumin and blood. Post-mortem findings included tabular necrosis and hyperemia of the kidneys (Brieger, 1920).

Only one of the above studies (Goldman and Karotkin, 1935) was available for review. It is difficult to determine if chromium has a direct toxic effect on the kidneys or alters the normal homeostasis of the body, thereby exerting its effect. Evidence to support the first view comes from a study conduted by Mutti et al. (1979). They examined welders and chromium platers, and found that workers with a higher degree of exposure to chromium showed a pattern of nephrotoxicity, as evidenced by increases in the indices for renal tubular damage. The length of exposure and concentration of chromium were not specified. It is interesting to note that the workers who had a higher degree of exposure to chromium also demonstrated higher urinary chromium values.

Pederson and Mersch (1978) reported the incident of a woman who ingested 10 mℓ of a 50-% chromic acid solution with 150 mℓ of Coca-Cola. Vomiting occurred several times in the hospital, where gastric lavage was performed and activated charcoal, magnesia, and milk were administered. Hemodialysis was initiated 18 hours after ingestion. Blood samples were consistent with anemia, which was most pronounced by the eighth day of hospitalization. Slight granulocytopenia was observed on the third day. There was significant proteinuria (1.9 g) on the first day.

Bilirubin levels rose during the first 3 days. One day after ingestion, the patient was admitted to the renal unit; the serum chromium was 1.37 μg/mℓ (2.94 mg Cr/ℓ whole blood). Dialysis treatment was instituted, which accelerated the removal of chromium from the serum. During the patient's stay, no signs of gastrointestinal or cerebral disturbance were noted. Hepatic function was normal upon discharge, following a hospital stay of 11 days.

7.5.3. Miscellaneous Toxic Effects. Mancuso (1951) reported that chromate workers frequently showed excessive susceptibility to inflammatory and ulcerative conditions of the gastrointestinal tract caused by ingestion of chromium.

Hepatic injury, apparently due to exposure to chromic acid mist from plating baths, has been reported (Pascale et al., 1952). One woman who had been employed for 5 years at a chromium plating factory was hospitalized with jaundice and was found to be excreting significant amounts of chromium. A liver biopsy specimen showed microscopic changes resembling those found in toxic hepatitis. Eight coworkers were screened for urinary chromium excretion in an effort to investigate the possibility that the hepatic damage was of occupational origin. Four of the workers were found to be excreting significant amounts of chromium. In three workers who had been exposed to chromic acid mists for 1 to 4 years, liver biopsy specimens and a series of 12 hepatic function tests showed mild to moderate abnormalities. The correlation of degree of hepatic injury with the concentration of chromic acid mist and information on controls were not available.

Frenkiel and Albert (1976) reported that traumatic injury of the tympanic membrane and external auditory canal, and changes in middle ear mucosa were suffered by a worker who had fallen into a vat of chromic acid. Extensive chemical burns were sustained, along with a 20 decibel conductive hearing loss stemming from an acid burn to the right tympanic membrane.

7.6. SUMMARY OF TOXIC EFFECTS OTHER THAN CANCER FOLLOWING EXPOSURE TO CHROMIUM COMPOUNDS

Inhalation is both the most predominant route of exposure to chromium compounds in industry, and the route most extensively investigated. Local effects on the respiratory system are the primary toxic effects observed in workers exposed to chromium in the atmosphere. Cr(VI), in the form of chromic acid, has been associated for many years with the development of perforations of the nasal septum. The implication of chromic acid as the causative agent results from the common occurrence of this disorder in the chromium-plating industry, where exposure is restricted to this Cr(VI) compound. Other Cr(VI) compounds may also participate in the etiology of perforated nasal septums, since this disorder has been reported in the chromate manufacturing industry, where the predominate exposures are to Cr(III) and the Cr(VI) compounds, sodium chromate and sodium dichromate; however, chromic acid mist may also be present in these plants. It is interesting to note that nasal septum perforation has not been reported as an occupational hazard in the chrome leather tanning industry or the chrome pigment industry, both of which exclusively use Cr(VI), although these industries are associated with severe chromium dermatitis. The lack of perforated nasal septums in these industries may result from differences in the physical or chemical form of the chromium, droplets in the tanning industry and particulates in the pigment industry as compared to the chromic acid mist generated in the plating industry. The measurements of chromic acid associated with perforated septums in the chrome-plating industry is ≥ 0.1 mg/m^3 (see Table 7-26); however, it is not known if lower concentrations are also effective. Also, severe irritation of the throat and lower respiratory tract have been associated with chromium compounds at concentrations as low as 0.12 mg/m^3. Again, as with perforated nasal septum, this respiratory tract irritation is primarily associated with Cr(VI). Hyper sensitivity may result from dermal or inhalation exposure to either Cr(VI) or Cr(III); however, there is little information available on the levels of exposure necessary to induce an allergic response.

Little information is available on systemic effects of inhalation of chromium compounds, although Pascale et al. (1952) and Mutti et al. (1979) reported liver injury in a chromate worker and kidney injury in a welder exposed to chromium, respectively. Acute exposure of animals using a variety of routes of administration (Section 7.1.2) have indicated that both Cr(VI) and Cr(III) compounds can produce kidney and liver damage, although the dose levels employed were relatively high. From the evidence available from both human case reports and animals studies, it can only be speculated whether the kidneys and liver may be target organs following chronic exposure to chromium compounds.

Although inhalation studies of occupational exposure to chromium indicate that exposure to some chromium compounds can result in perforation of the nasal septum, irritation of the respiratory tract, pneumoconiosis, bronchitis, chronic lung congestion, and possible liver and kidney damage (as supported by target organ toxicity in acute animal studies), there are insufficient data available to make a quantitative risk assessment for either chromium as a class or individual chromium compounds from these inhalation studies. The only studies that provide any exposure data are the studies of the occurrence of perforated nasal septums. However, these are of limited and questionable quality, since measurements were not made contemporary with exposure and personal habits, such as picking of the nose, may result in high local concentrations of chromium. Since perforated nasal septum results from the local destruction of the mucous membrane of the nose, this does not represent a systemic effect of chromium. Also, in the study by Nettesheim et al. (1971), inhalation exposure of mice to chromium resulted in marked effects to the respiratory tract. These effects, including hyperplasia and necrosis, were likely to have resulted from the severe local irritation of the cells lining the air ways. It would not be expected that exposure to chromium by any other route would result in this disorder, and although these data can be used to derive an acceptable inhalation exposure level, they are inadequate for determining safe levels of chromium by all routes of exposure. The limited information on other systemic effects of inhaling chromium, liver and kidney damage, contains both insufficient exposure data and too few case reports to form a firm association between exposure and effect.

There are only a few instances of human exposure to overtly toxic levels of chromium compounds by ingestion, and these represent acute exposure to massive doses which provide little information on the safe levels of chromium following chronic exposure. A number of animal studies have been performed in which the chromium compound was administered in the food, water, or by gavage. The acute oral toxicity data indicate that Cr(VI) is approximately 2 or 3 orders of magnitude more toxic than Cr(III), with the latter toxic at the level of g/kg body weight (Section 7.1.2). The difference in valence state may be less relevant following chronic or subchronic ingestion of chromium, since it is suggested that Cr(VI) is reduced to Cr(III) under the acid conditions of the stomach. The determination as to whether Cr(III) or Cr(VI) is more toxic after chronic exposure, however, cannot be made, since none of the studies employed a sufficiently high dose to produce a toxic effect.

The only ingestion study in which an effect was observed was that of Ivankovic and Preussman (1975) in which rats were fed diets containing 2 or 5% $Cr_2O_3 (Cr^{+3})$, 5 days/week for 90 days. The only observed effect was a reduction in the weight of the liver and spleen in the treated male rats as compared with liver and spleen weights of control animals. Similar results were observed in female rats maintained on the same diet. Neither organ showed macroscopic or microscopic abnormalities, and the authors concluded that these changes were not toxicologically important. In a larger 2-year study using the same experimental procedure and 60 animals of each sex per group, Ivankovic and Preussman (1975) did not mention any treatment-related changes in organ weight, although it was mentioned that no signs of chronic toxicity were observed. Therefore, it is unclear whether the slight change in organ weight observed in the small number of animals in the 90-day study was the result of spurious observation due to the small group size, or whether the 5% exposure level represents a true NOAEL (no-observed-adverse-effect-level). No matter whether this 90-day study represents a NOAEL or an NOEL (no-observed-effect-level), the small group size makes this study very tenuous as the basis for quantitative risk assessment.

While chromium compounds have been shown to cause developmental toxicity in experimental animals, the reproductive effects (e.g., fetal malformation) were observed only where maternal toxicity was also present. Because of the unnatural routes of exposure in these studies (e.g., intravenous and intraperitoneal injection), the relevance of these developmental effects to environmental exposures is very uncertain; more research is indicated to better understand the implications of different levels and routes of exposure.

In the absence of any data on effect levels following chronic exposure to chromium, the U.S. EPA, in the Ambient Water Quality Criteria Document for Chromium (U.S. EPA, 1980a), derived acceptable daily intake values (ADIs) of 0.175 and 125 mg/day/man for Cr(VI) and Cr(III), respectively. These ADIs were derived by using the highest NOEL available for each valence state. For Cr(VI), the study of MacKenzie et al. (1958) was used, in which rats were exposed to several levels of chromium in the form of K_2CrO_4 up to 25 ppm in the drinking water for 1 year, while for Cr(III), the chronic study of Ivankovic and Preussman (1975) was used, in which rats were fed diets containing up to 5% Cr_2O_3 for 2 years. The ADIs for both Cr(VI) and Cr(III) were expressed as mg/d of the compound administered. Although these ADIs were derived, it is not apparent from the toxicologic information available whether the ADIs are more appropriate for the specific chromium compounds tested, K_2CrO_4 and Cr_2O_3, rather than the general classes of Cr(VI) and Cr(III). This is particularly hard to determine, since no toxic effects were observed in these chronic animals studies.

8. CURRENT REGULATIONS AND STANDARDS

A number of recommended standards presently exist for permissible levels of chromium in both air and water. The National Academy of Science (NAS, 1980) and the U.S. Environmental Protection Agency (U.S. EPA, 1980a), in regard to ambient water quality criteria, have stated that a distinction between the Cr(III) and (VI) forms should be made when considering the formulation of regulations and exposure criteria.

8.1. OCCUPATIONAL EXPOSURE

NIOSH (1973, 1975), OSHA (1978), and ACGIH (1981) have recommended various exposure limits for chromium. These values are based on the chemical form of the chromium compounds or their solubilities. Table 8-1 outlines the various United States occupational standards for chromium compounds.

8.2. EXPOSURE TO CHROMIUM IN AMBIENT WATER.

A number of standards exist for chromium in ambient water or drinking water. In general, the standards for occupational exposure to chromium in the air allow for a greater uptake of chromium than by the uptake of chromium from drinking water. The U.S. EPA (1980a) has estimated the daily intake of chromium from drinking water to be 5 μg/day. Table 8-2 outlines various recommended or established standards for chromium in the United States.

The U.S. EPA (1980a) recently proposed several ambient water quality criteria for chromium. Based on methodology outlined in the Federal Register (45 FR 79353), acceptable daily intakes (ADIs), no-observable-adverse-effect levels (NOAELs), and bioconcentration factors (BCFs) obtained from experimental animal studies, separate water quality criteria were proposed. Table 8-3

TABLE 8-1

Recommended Occupational Standards and Recommended Criteria for Chromium Compounds in the United States

Chemical Form	Standard ($\mu g/m^3$)	Reference
Non-carcinogenic chromium (VI)[a]	25 TWA[b] 50 Maximum	NIOSH, 1975
Carcinogenic chromium (VI)[c]	1	NIOSH, 1975
Chromic acid (as chromium trioxide)	50 TWA 100 Maximum	NIOSH, 1973
Soluble chromic or chromous salt	500 TWA	OSHA, 1978
Insoluble salts or chromium metal	1000	OSHA, 1978
Chromium metal	500 TWA	ACGIH, 1981[d]
Chromium (II) compounds	500 TWA	ACGIH, 1981
Chromium (III) compounds	500 TWA	ACGIH, 1981
Chromium (VI) compounds		
water soluble	50 TWA	ACGIH, 1981
water insoluble[d]	50 TWA	ACGIH, 1981
Chromite ore[e]	50	ACGIH, 1981
Chromium: soluble chromic and chromous salts	500 TWA	ACGIH, 1981

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[a] NIOSH listed "non-carcinogenic" chromium VI compounds as the monochromates and dichromates (bichromates) of: hydrogen, lithium, potassium, rubidium, cesium, ammonium, and chromic oxide (chromic acid anhydride).

[b] Time Weighted Average

[c] NIOSH listed "carcinogenic" chromium VI compounds as all other chromium compounds not included in the "non-carcinogenic" chromium VI listed above.

[d] These are also known as the TLV values established by ACGIH.

[e] ACGIH listed these classes of chromium compounds as substances associated with industrial use that have been recognized as carcinogens.

TABLE 8-2

Recommended Standards for Chromium
in Ambient Waters in the United States

Chemical Form	Medium	Criteria (μg/ℓ)	Reference
Chromium (VI)	drinking water total	50	U.S. Public Health Service (USPHS), 1962
Total Chromium	domestic water supply	50	U.S. EPA, 1976
Total Chromium	freshwater (aquatic life)	100	U.S. EPA, 1976
Chromium (VI)	livestock water	1000	National Academy of Science and National Academy of Engineering (NAS/NAE), 1972
Chromium	community water systems and non-community water systems	50	40 CFR 141.11

TABLE 8-3

Ambient Water Quality Criteria for the Protection of Human Health[a]

Chemical Form	NOAEL (mg/ℓ)	Rat NOAEL (mg/d/kg)	ADI for man (mg/d/man)	BCF	Calculated Criteria (µg/ℓ)
Chromium (III)[b]	50,000	1786	125	16	59,000
Chromium (VI)	25	2.50	0.175	16	83

[a] Source: U.S. EPA, 1980a

[b] Revised ADI and criterion. Published values (45 FR 79331) were incorrect. If exposure to trivalent chromium results only from the eating of fish and shellfish, then the calculated ambient water criterion for chromium (III) is proposed as 1200 mg/ℓ (1.2×10 µg/ℓ)

summarizes the proposed U.S. EPA (1980a) ambient water quality criteria for the protection of human health.

The U.S. EPA (1980a) also has proposed several ambient water quality criteria for the protection of aquatic life. Table 8-4 summarizes the proposed criteria for the protection of aquatic life.

8.3. EXPOSURE TO CHROMIUM IN AMBIENT AIR.

No federal or state (other than the state of Maine, i.e., 0.05 $\mu g/m^3$ for mean annual and 0.3 $\mu g/m^3$ for mean daily limits) ambient air chromium standards have been proposed. No United States emission standards for chromium were found in the available literature. The U.S.S.R. recommends a "sanitary clearance zone" of 1000 m for plants discharging 200 kg Cr(VI) per day, and 2000 m for plants discharging 1000 kg per day (NAS, 1974).

TABLE 8-4

Calculated Ambient Water Quality Criteria for the Protection of Aquatic Life*

	Freshwater Life		Marine Life	
Chemical Form	24-hour Average (μg/ℓ)	Maximum (μg/ℓ)	24-hour Average (μg/ℓ)	Maximum (μg/ℓ)
Chromium (VI)	0.29	21	18	1260
Chromium (III)	44 (chronic value toxicity)	NR	10,300 (acute toxicity value)	NR

*Source: U.S. EPA, 1980a
NR = Not recorded

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